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# A.M.A. ARCHIVES OF SURGERY

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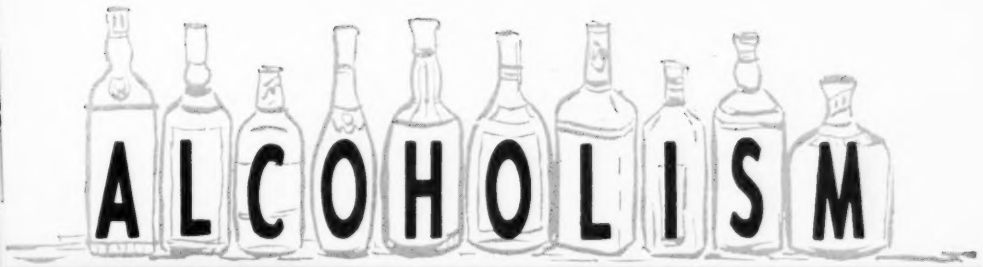


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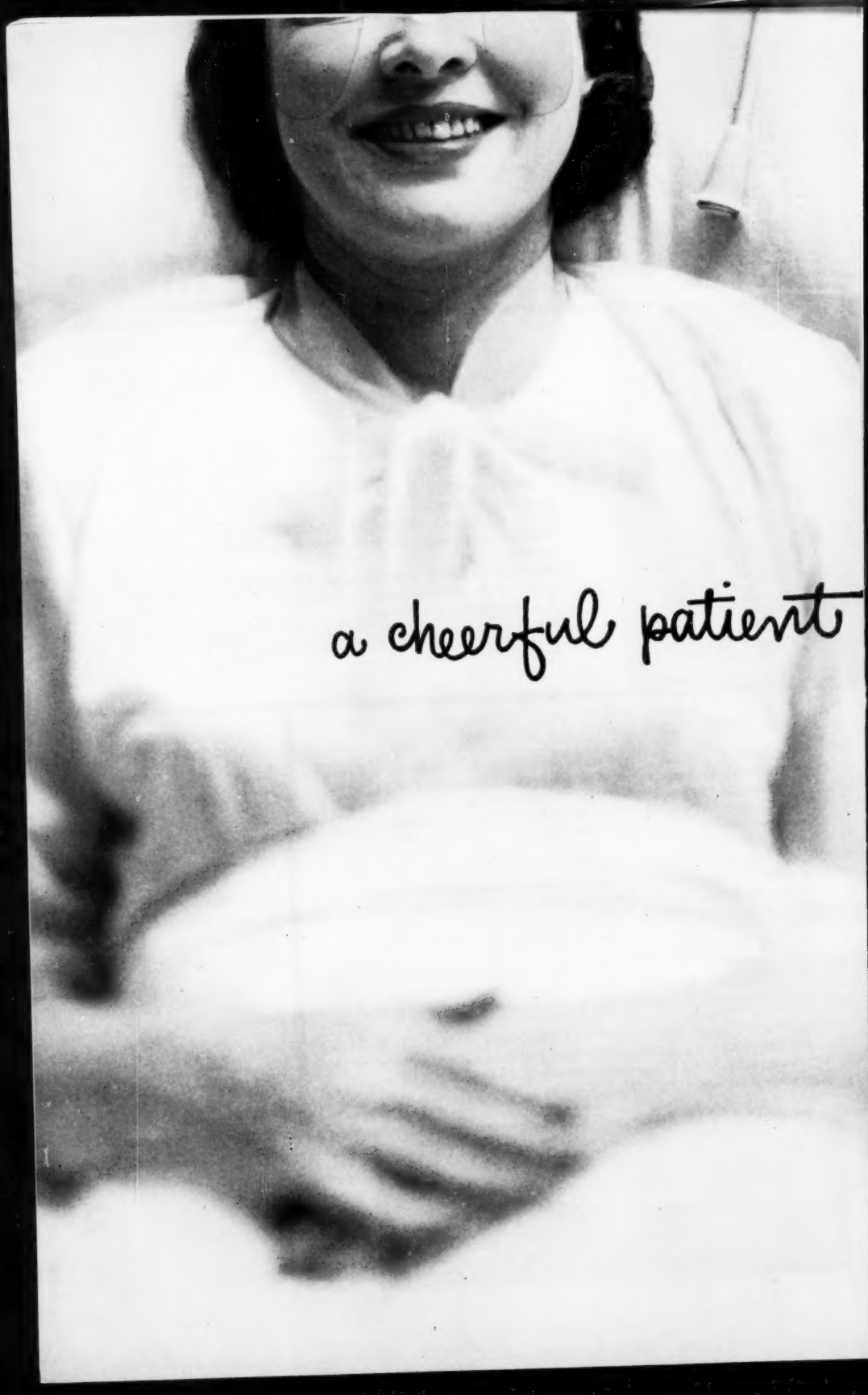
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# Motion Pictures in Medical Education, with Particular Reference to the Undergraduate Phase

HILGER PERRY JENKINS, M.D., Chicago

In the graduate and postgraduate phases of medical education the value of motion pictures has become well recognized. However, in undergraduate medical education this is not fully appreciated as yet. My thesis is essentially "that every medical student should have an opportunity to see in good color motion picture photography every disease or condition about which he should be expected to know something, accompanied by discussion from his teacher appropriate to the importance of the subject."

It is generally conceded that the ideal in teaching is to have the student see personally as many clinical problems as possible, with an opportunity to take a history and examine and closely follow the patient with the aid and counsel of the teaching staff. Small discussion groups at the bedside or in conference rooms add further to this highly personalized type of teaching. Teaching such as this requires a great deal of time and energy of the student, as well as the teacher. There is a limit to the number of clinical problems which can be covered in this way. The vastness of the subject matter of a modern medical education suggests a need for improving the efficiency of teaching methods so that the student may more readily grasp and retain in proper perspective the enormous store of knowledge he is presumed to have acquired when he graduates as a doctor of medicine.

There is a tremendous opportunity to increase very substantially the efficiency of our teaching in the medical schools by the judicious use of motion pictures. This could be done in three ways.

1. In the preclinical years a comprehensive survey course with motion pictures could be given. Appropriate commentary by the teacher would provide an excellent background for a better understanding of the problems which will be confronted in the clinical years. This might be punctuated with suitable case demonstrations from available clinical material, which would be in keeping with some current trends in medical education. This could be called a preclinical cinematic *survey*.

2. During the clinical years, when most of the teaching is done at the bedside or in clinics or conferences, with the use of individual cases to illustrate the important aspects of medicine, there would be an excellent opportunity to use motion pictures. One could show the many variations in the disease under discussion, as well as the lesions which might be considered in the differential diagnosis. This could be

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Chairman, Motion Picture Committee, American College of Surgeons.

From the Department of Surgery, University of Illinois College of Medicine.

Presidential Address, given at the 15th Annual Assembly of the Central Surgical Association, Feb. 21, 1958.

called a cinematic embellishment, or *supplement,* to the basic clinical teaching.

3. During the senior year the less common clinical problems, which should be a part of every student's knowledge, could be presented in motion pictures whenever suitable clinical material is not available. This could be called a cinematic *substitute* for clinical material.

In considering a rather broad use of motion pictures in medical education the role of the teacher in such a plan must be considered. The effectiveness of motion pictures can be measured only in terms of the use the teacher makes of the films. For the principal part of the curriculum it is absolutely essential that the teacher take the leadership in planning the course, with a view to taking advantage of such photographic material as is available to augment his presentation of the subject. Mechanization of education, or "pedagogical automation," leaves much to be desired, for nothing on the screen or on a sound tract can make up for the personal influence of the teacher on the student, a relationship which must not be disturbed. However, this must not be confused with the judicious use of "mechanized" audiovisual aids, as this is essential to progress in the field of education generally.

I should like to pay tribute to the authors of a number of surgical films which have a sufficient breadth of educational value to be admirably suited for undergraduate teaching purposes. Most of these films have been presented on the program of the American College of Surgeons. Although this program is essentially in the category of postgraduate education, there is emphasis here on basic teaching value. Most of the films to be mentioned could well be shown in their entirety; a few might be shown in part. Many others, not included here, contain valuable teaching material which might be condensed into shorter versions for undergraduate purposes.

First of all in the field of trauma, which promises to be ever expanding in importance, the following films deserve mention: Head Injuries by Davis [1]; Thoracic Injuries by Noer [2]; Hernia of Diaphragm by Adams, Reynolds, and Moulder [3]; Abdominal Injuries by Kredel [4]; Tendon Injuries by Mason [5]; Multiple Injuries by Hardy [6]; Transportation of the Injured by Curry [7], and the Fracture series by Larmon.[8]

In orthopedics the series on Surgical Approaches to the Joints, by Abbott,[9] is very impressive. The anatomical drawings presented here and in the Larmon films have a high educational value as such, regardless of the clinical aspects of the subject for which they represent background. A number of films on Surgical Anatomy should be mentioned, such as those by Baumgartner,[10] Bergman,[11] and Moseley.[12]

In pediatric surgery, the several films by Potts [13] cover a number of problems in this field and could be used in either a survey or a substitute category, particularly in schools where clinical facilities may be limited, for this type of work. Another series of films on pediatric surgery will soon be available from Lynn and Noer.

In the field of cardiovascular surgery, where so many films are now being produced primarily to illustrate new techniques, there are a number which have a basic educational value. The group of films by Humphreys [14] represents a prodigious pedagogical effort to correlate embryology, physiology, and pathology of the circulatory system. Another series, by Rushmer,[15] is deserving of special mention. The unique demonstration of the action of the heart valves by Klassen [16] contributes to a better understanding of the heart as related to disease of the valves. The films by Jones [17] on Coarctation and on the Tetralogy of Fallot very nicely combine the surgical features with the basic aspects of these conditions. The recent developments in surgery of the aorta are magnificently portrayed in several films by De Bakey and Cooley.[1] Although these are primarily for graduate and postgraduate audiences, they are so well embellished with diagrams and anima-

tion and are so spectacular in nature as to warrant their use in undergraduate teaching.

In general surgery, a variety of subjects are especially well presented and could be used to advantage in one of the three ways mentioned, i. e., survey, supplement, substitute. The films on Diseases of the Breast, by Price,[19] would be excellent for a preclinical survey course. As embellishment or supplement to case presentations in clinics or conferences, to provide an illustrative phase of the discussion of the subject, the following films are excellent: Polyps of the Colon by Holden[20]; Rectal Prolapse by Judd[21]; another on Rectal Prolapse by Altemeier[22]; Carcinoma of the Lung by Adams[23]; Complicated Appendicitis by Rives[24]; Diverticulitis by Gilchrist[25]; Ulcerative Colitis by Patterson.[26]

For the less common diseases, which may not be represented by available clinical material but which are of sufficient importance to warrant some discussion by the teacher, there are numerous suitable films. There are four which are especially outstanding in this category: Volvulus by Wilson[27]; Putz-Jeager Syndrome by Waugh[28]; Pancreatic Cysts by Puestow,[29] and Subdiaphragmatic Abscess by Bradshaw.[30] Quite a few films of the less common clinical entities are added to the Library of the American College of Surgeons each year from the annual program on unusual and spectacular surgical problems.

In the field of gynecology there are three excellent films: Ovarian Tumors by Schmitz[31]; Endometriosis by Allen,[32] and Lesions of the Fallopian Tubes by Philpott.[33] In urology, the Story of Renal Calculi by Higgins is very good.[34] The series of films by Hollinger[35] is especially unique. The vivid endoscopic cinematography of the larynx, trachea, bronchus, and esophagus portrays the diseases thereof in such a way that for teaching purposes the films are much better than anything the untrained eye could possibly see through an endoscope. Here, indeed, is a good example of a cinematic substitute, i. e., for clinical material, which has such a fundamental teaching value as to be admirably suited for undergraduate education.

The discussion of important subjects such as burns can be nicely implemented by motion pictures. The film by Ellison is apparently filling this need widely, judging from the very large number of requests for its use.[36]

Special mention is due the magnificient animated film on Embryology and Pathology of the Intestinal Tract by Chaffin.[37] This 14-minute award-winning cinematic masterpiece is valuable for teaching from the freshman to the senior year, as well as thereafter. It would be especially well suited for a preclinical survey course.

Finally, I should like to mention a film which in my opinion shows how beautifully an operation can be performed, with all the niceties and refinements of surgical technique which every medical student should have an opportunity to see. This is none other than the award film on Splenectomy by our host and immediate past president, Dr. Robert Zollinger.[38]

I have been personally interested in the filming and editing of medical motion pictures. The principal purpose of these films is to show the nature of surgical disease as seen in the operating room, in the surgical pathology laboratory, or in the morgue. X-rays and diagrams, some with animation, are added, along with brief clinical data and a minimum of explanatory titles. Thus far, 13 films have been produced and are available from film libraries.[39] These are all relatively short films, averaging about 15 minutes. The subtitle, "Photographic Supplement for Clinics or Conferences," suggests the manner in which they can best be used. They are without sound, to permit the lecturer or conference moderator to add whatever comment he wishes during the showing of the film. The titles do not attempt to cover the subject matter, which is the province of the teacher to discuss as best suits the audience.

The following films would be useful in a survey in the preclinical years, as well as a conference or lecture supplement in the clinical years: Diseases of the Gallbladder; Diseases of the Stomach and Duodenum; Diseases of the Appendix; Diseases of the Small Intestine. In addition, the following would also fit into this group: Acute Pancreatitis; Hemorrhage from Duodenal Ulcer; Mesenteric Thrombosis and Adhesion-Band Strangulation; Carcinoma of the Cecum; Polyps of the Large Intestine, and Strangulated Femoral Hernia. In the substitute category, i.e., for clinical material the following would be useful: Intestinal Obstruction Due to Ascaris Lumbricoides; Gallstone Ileus, and Gastrojejunocolic Fistula.

Excerpts from these films, as well as from a large collection of unedited motion picture films, will be shown to illustrate the value of motion pictures in medical education.

Twenty-one subjects were briefly portrayed in motion pictures, in 11 minutes, with the following comments:

1. Absorbable gelatin sponge (Gelfoam) "Patch" for Control of Hemorrhage. In this first sequence a small, compressed patch of Gelfoam is used to control hemorrhage from a wound of the inferior vena cava in an experimental animal. The manner in which this rather dynamic and spectacular control of hemorrhage is portrayed under experimental conditions led me to explore the possibilities of using motion pictures to record all interesting cases which might be of teaching value.

2. Gastric Ulcer. In this sequence an ulcer is demonstrated in the region of the pyloric antrum. Artist's drawings of the stomach, with identification of landmarks and pathology, and insert to correspond with what would be expected in the x-ray after a barium meal, and, finally, the x-ray, are thrown on the screen in rapid succession to aid in correlating the pathology with the x-ray. This type of film would be especially useful in a preclinical survey course or as a supplement to a case demonstration of gastric ulcer.

3. Hemorrhage from Duodenal Ulcer. In this brief portrayal of the pathology of a large duodenal ulcer which has eroded an artery, the magnitude of hemorrhage which may occur is demonstrated by perfusing citrated blood through the eroded artery to simulate the hemorrhage which had been the cause of death. This type of film would help to emphasize the seriousness of this complication of ulcer.

4. Leiomyosarcoma of the Stomach. One of the unusual lesions of the stomach is demonstrated in such a way that one would easily recognize it again because of its characteristic appearance.

5. Cardiospasm. This demonstration at autopsy of the dilated esophagus characteristic of this disease should be helpful in a better understanding of this clinical problem. Autopsy photography could well be used more frequently by the clinical teacher when it best serves the purpose of clarifying the nature of the disease under discussion.

6. Intestinal Obstruction Due to Ascaris Lumbricoides. This rather unusual cause of obstruction is still a clinical entity which one must be prepared to recognize, especially in persons recently migrated from areas where ascariasis is prevalent. The removal of the ascarid from the intestine makes a rather dramatic demonstration, which is not easily forgotten. In the complete film there are x-rays and a case history, and the life cycle is presented in simple animation.

7. Mesenteric Thrombosis. The demonstration of this disease as seen at surgery, as well as in the surgical pathology laboratory, should be helpful in a better understanding of this problem when it is the subject of discussion.

8. Strangulation Obstruction with Gangrene. The portrayal of the black, necrotic bowel which has been strangulated by a tiny omental band is an excellent way in which to supplement a lecture or conference on causes of acute obstruction or to illustrate

one of the limitations of the use of the long intestinal tube for decompression of distended obstructed bowel.

9. Regional Enteritis. This disease has been well reviewed recently in the lay press and on television. It would be desirable for all medical students at least to see a good example of regional enteritis in motion picture film, as relatively few will have an opportunity at the operating table to get a really good look. Futhermore, the correlation of the x-ray and the pathology, with the help of overlays which identify landmarks and the location of the pathology, is helpful in the understanding of the significance of the "string" sign.

10. Lymphosarcoma of the Ileum. This is not very common but should be included at least in the differential diagnosis of regional enteritis, which it may at times simulate. This brief demonstration should add to the discussion of this problem.

11. Leiomyosarcoma of the Jejunum. This uncommon lesion deserves mention at least in the elaboration of the causes of melena. Its characteristic appearance as seen in motion picture photography would be more helpful in diagnosis at the time of surgery than most frozen sections.

12. Suture of Wound of the Intestine. Suture techniques can be more clearly demonstrated on resected bowel with the help of some of the devices which are permissible in motion picture photography, but which might require more time than would be permissible or desirable at the operating table. The use of multiple single frames alternating with ordinary photography makes possible demonstrations of technique which should be most helpful.

13. Gallstone Ileus. A gallstone is a rather infrequent cause of small-bowel obstruction but must be seriously considered as a possibility in the very elderly patient. Four cases are recorded in film, and for this presentation the etiology is shown in diagrams and animation.

14. Hydrops of the Gallbladder. In any discussion of gallbladder disease in which a case is presented it would be desirable to show various manifestations of the disease, of which hydrops is one. In this example of hydrops, the clear fluid content of the gallbladder, the stones, especially the one impacted in the cystic duct, all add to a better comprehension of this particular type of gallbladder disease. In the complete film, empyema, fistula, gangrene, and carcinoma are included.

15. Pyogenic Granuloma. The appearance of this simple superficial lesion should be brought to the attention of every medical student, lest it be confused with malignancy.

16. Malignant Melanoma. The characteristic dark-blue color of the lesion of the leg which is shown and the coal-black metastatic lymph nodes in the groin provide a good visual introduction to a discussion of this subject.

17. Nonpigmented Malignant Melanoma of the Toe. This neglected ulcerated lesion of the toe and the pulmonary metastases seen in the x-ray provide a suitable reminder that small superficial lesions should not be underestimated.

18. Torsion of the Testis. The demonstration of the necrotic testis after incision of the scrotum should help in establishing the importance of torsion of the testis. It should help to remind one that pain in this area is not necessarily due to epididymitis or orchitis.

19. Twisted Ovarian Cyst. Whenever one discusses the diagnosis of the acute abdomen, the twisted, infarcted cyst of the ovary is conventionally one of the items to consider. A good demonstration of this, as well as other lesions producing abdominal pain, would be most helpful in covering this very important and broad subject.

20. Ruptured Tubal Pregnancy. Here, again, is another cause of acute abdominal pain which can be rather dramatically portrayed in film.

21. Fetus with Amniotic Sac. In this final sequence, a 12 mm. embryo in its amniotic sac is shown. It had been extruded from a tubal pregnancy. The

significance of this in extrauterine intra-abdominal pregnancy which may go on to term could be covered, with this as an illustration of how it began.

In concluding this cinematic demonstration, it would be well to emphasize again that the student can best grasp the full significance of surgical disease if he has an opportunity to see personally at the operating table and in the surgical pathology laboratory the nature of the disease which is the subject of the discussion. This type of personal experience cannot possibly cover all the problems with which the student should be familiar. Motion pictures most nearly approximate the personal experience. Why not cover the surgical curriculum in motion pictures, or, for that matter, all the subject matter of a modern medical education which can be recorded in this way?

There are many who are interested in expanding the use of motion pictures in medical education. Under the able leadership of Ralph Creer, the motion picture program and film library of the American Medical Association has contributed substantially to progress in cinematic education. The Library of the Medical Audio-Visual Institute of the Association of American Medical Colleges is another important factor for progress in this field. Dr. David Ruhe contributed to the development of this Association's library. This and his present activities as director of the department of audiovisual education at the University of Kansas are well recognized. Dr. J. Edwin Foster has subsequently made notable advances in this Association's film department during his term of office as director of their Medical Audio-Visual Institute.

The motion picture activities of the American College of Surgeons have been largely implemented by Dr. H. P. Saunders (with all due respect to the chairman of the Motion Picture Committee). An important factor in the College program has been the Cine Clinics, sponsored by the American Cyanamid Company, Surgical Products Division (formerly Davis & Geck, Inc.). The photographic department of this Company has produced 10 to 20 films a year since 1951. An attempt was made in most of these productions to present a surgical subject in which the operation was only a part. Emphasis has been placed on the use of x-rays, diagrams, and surgical specimens to implement the covering of the subject and thus enhance the breadth of educational value. The added feature of the introduction of the author on the screen at the beginning of the film for his preliminary remarks has made for a personalized, rather than a mechanized, type of presentation. Thus far, 120 of America's leading surgeons, including a few from the British Commonwealth, have participated in a Cine Clinic. Another 16 or more films will be ready this year. Nearly every chairman of a surgical department of our medical schools and large clinics is included, and needless to say, the films represent a most valuable collection of teaching material. This type of surgical motion picture production was started under the direction of Carol Adams and has been continued and expanded by Edwin Lewis.

Another important part of the College motion picture activities has been the stimulating of independent productions from the medical schools and clinics, which are shown at the Clinical Congress. To facilitate the distribution of these valuable films to teaching institutions, the Library of the American College of Surgeons was started three years ago. A substantial grant from the Ethicon Suture Laboratories has made this Library possible.

The professional medical motion picture studios deserve a great deal of credit for producing some of the most elaborate teaching films, with animation and special photographic effects, which contribute to the value of the film. Sturgis-Grant, Churchill-Wexler, Mervin LaRue, Billie Burke, and others have indeed set a very high standard for motion pictures in medical education.

## Summary

There is a vast opportunity to improve the efficiency of our basic clinical teaching methods in undergraduate medical education by the judicious use of motion pictures.

This could be done by the selection of films which would be useful in the three following categories: preclinical *survey; supplement* to clinics or conferences, and *substitute* for clinical material which may not be available.

An incomplete list of films which in my opinion would be of value in the undergraduate teaching of surgery is presented.

Motion pictures must always remain the servant of the teacher. "Pedagogical automation" cannot replace the personal influence of the teacher on the medical student. However, the judicious use by the teacher of "mechanized" audiovisual aids makes for progress in education.

## Conclusion

The full utilization of motion pictures might well bring a broader and more valuable experience to the medical student than could be obtained by an additional 1000 beds in the teaching units of the university hospitals.

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A. M. A. American Medical Association Motion Picture Library, 535 N. Dearborn St., Chicago 10

C. M. E. College of Medical Evangelists, Department of Visual Education 720 Brooklyn Ave., Los Angeles 33

C-W. F. P. Churchill-Wexler Film Productions 801 N. Seward St., Los Angeles 38

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* All films in this series are also available from Veterans' Administration, Central Office Film Library, Vermont Ave. and H St., Washington 25, D. C.

† A. C. S. Award 1952 for this entire series of films. All films in this series are also available from Veterans' Administration, Central Office Film Library, Vermont Ave. and H St., Washington 25, D. C.

The following films from this series are available also from American Academy of Orthopedic Surgeons, 116 S. Michigan Ave., Chicago 3:

Surgical Approaches to the Scapulohumeral Joint

Surgical Approaches to the Elbow Joint

Surgical Approaches to the Joints of the Foot

Surgical Approaches to the Hip Joint

Surgical Approaches to the Knee Joint

Surgical Approaches to the Spine and Sacroiliac Joint

# Studies During the Immediate Postoperative Period Following Total Body Perfusion

EDWARD C. MATTHEWS, M.D.; LELAND C. CLARK, Ph.D.; F. KATHRYN EDWARDS, M.D.; SAMUEL KAPLAN, M.D., and JAMES A. HELMSWORTH, M.D., Cincinnati

In the period immediately following total body perfusion for open cardiotomy, careful evaluation and management of the patient is required. While physiologic studies carried out during this period are designed principally to give proper direction to the postoperative care of the patient, they may also be used as a measure of the adequacy of perfusion and the functional state of the cardiopulmonary systems.

## Materials and Methods

The data to be presented were obtained during perfusion and in the immediate postoperative period in a group of 10 consecutive patients operated upon for a variety of congenital cardiac defects. One of the patients was mildly cyanotic; the other nine were acyanotic. The patients ranged in age from 1 to 15 years and in weight from 6 to 43 kg. With all patients the Clark oxygenator pump[1] was used. The period of total body perfusion varied from 15½ to 59 minutes. Seven of the patients were operated upon with the heart in sinus rhythm, and in three patients potassium-citrate-induced cardiac arrest was used.

Incorporated into the pump is a monitoring chamber which permitted, during perfusion, continuous recording of pH, oxygen tension, and temperature of the pump-arterialized blood just before it was delivered to the patient. The pH was recorded by means of Beckman general purpose glass-and-fiber-type reference electrodes connected through a Beckman Model W Industrial pH Meter to a Brown Electronik recorder with a full-scale range set at pH 6 to pH 8. The electrodes, prior to use, were coated with silicone by exposing them to the vapor of General Electric Dri-Film (SC-87) and were calibrated in standard buffer. The oxygen tension of the arterialized blood was measured polarographically[2,3] and recorded on a suspension-type photoelectric galvanometer. Temperature of the arterialized blood was monitored continuously with a resistance thermometer.

Also during perfusion, venous blood, as it returned from the patient to the machine, was intermittently sampled for pH, oxygen saturation, and carbon dioxide content. The pH values were determined with the Model G Beckman pH meter, and the oxygen saturation and carbon dioxide content, by the Van Slyke manometric method.

In the postoperative period, samples of arterial blood were obtained from all patients at approximately hourly intervals for a period of four to six hours from the time the pump was turned off for determination of pH and oxygen tension, and in six of the patients carbon dioxide content and tension were also measured. The same electrodes used in the pump during perfusion served for the measurement of pH and oxygen tension in the postoperative period. The calibration of the pH electrode was checked in standard buffer between each of the postoperative determinations. The polarographic electrode was calibrated using a sample of blood equilibrated with room air. These determinations were carried out at 37 C in a water bath which is incorporated into the pump and used, during perfusion, to maintain normal blood temperature. Postoperative carbon dioxide contents were determined with a Kopp-Natelson Microgasometer[4] and the carbon dioxide tensions calculated from the nomogram of Dill, Edwards, Consolazio.

Minimum acceptable perfusion rates were determined for each patient by reference to a graph (Fig. 1) designed to indicate the perfusion rate necessary to maintain a venous oxygen saturation of 50%, assuming 100% arterial oxygen saturation and normal temperature and pH of the arterial

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From the Children's Hospital Research Foundation and the Departments of Pediatrics and Surgery, University of Cincinnati College of Medicine, and from the Fels Research Institute for the Study of Human Development, Antioch College, Yellow Springs, Ohio.

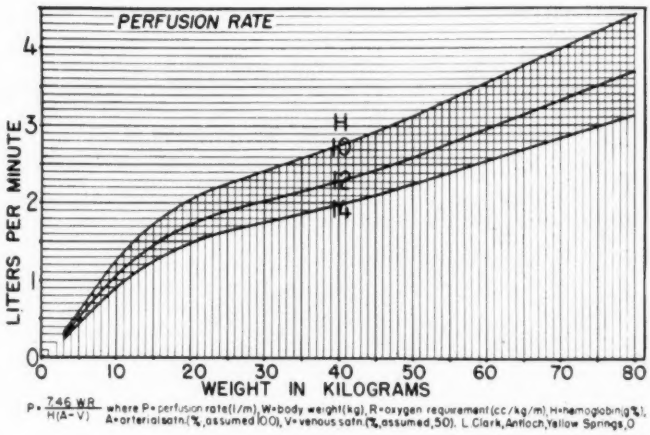


Fig. 1.—Graph for the determination of perfusion rate to yield a venous oxygen saturation of 50%.

blood. The graph was constructed on the basis of reported basal oxygen consumption of subjects ranging from 3 to 80 kg. and contains provision for varying the perfusion rate in accordance with the hemoglobin of the blood being pumped. This hemoglobin value is determined during the period of partial cardiac bypass after there has been adequate mixing of the patient's blood and the blood used to prime the machine. In actual practice, the perfusion rates derived from the graph were increased by 3% to 13% in relation to the amount of coronary and bronchial artery blood aspirated from the heart and returned to the pump.

Blood pressure and central venous pressure were measured manometrically before, during, and after perfusion. Replacement of blood loss was guided by a combined evaluation of the blood pressure and venous pressure, coupled with estimations of blood loss on the drapes and actual measurement of blood aspirated from the chest and contained on sponges. In addition, radioiodinated-albumin blood volume determinations[5] were used to evaluate blood balance.

During the initial stages of thoracotomy, anesthesia was maintained with a mixture of nitrous oxide, oxygen, and ether or cyclopropane, and during the period of perfusion the lungs were manually ventilated with 100% oxygen saturated with water vapor.

## Results

Perfusion rates and resulting venous oxygen saturations are presented in Figure 2. The patients are arranged along the abscissa in order of increasing weights. Perfusion rates are graphed both in terms of cubic centimeters of blood per kilogram per minute and of grams of hemoglobin per kilogram per minute. Since the hemoglobin concentration of the blood determines its capacity to transport oxygen, it is felt that effective perfusion rates are more accurately expressed in terms of grams of hemoglobin per kilogram per minute than by the commoner designation of cubic centimeters per kilogram per minute. In this group of patients, the hemoglobin of the mixed patient and machine blood ranged from 11.4 to 13.9 gm. %, but for the individual patient this value did not vary significantly during perfusion. It is to be noted that relatively high perfusion rates were used, all patients under 15 kg. in weight being perfused at a rate in excess of 100 cc/kg/min., or 12 gm. Hb/kg/min. The reciprocal relation of perfusion rate to body weight reflects the fact that, with increasing age and weight, oxygen consumption per unit of body mass decreases. The mean values of venous oxygen saturation ranged from 55% to 82%, with an average value for all patients of 69%. In the multiple samples taken from any single patient, the maximum variation in venous oxygen saturation was 10%. The fact that venous oxygen saturations were in excess of 50% is to be expected, since all patients were perfused in excess of the calculated rate and, in addition, oxygen consumption during anesthesia is less than that in the basal

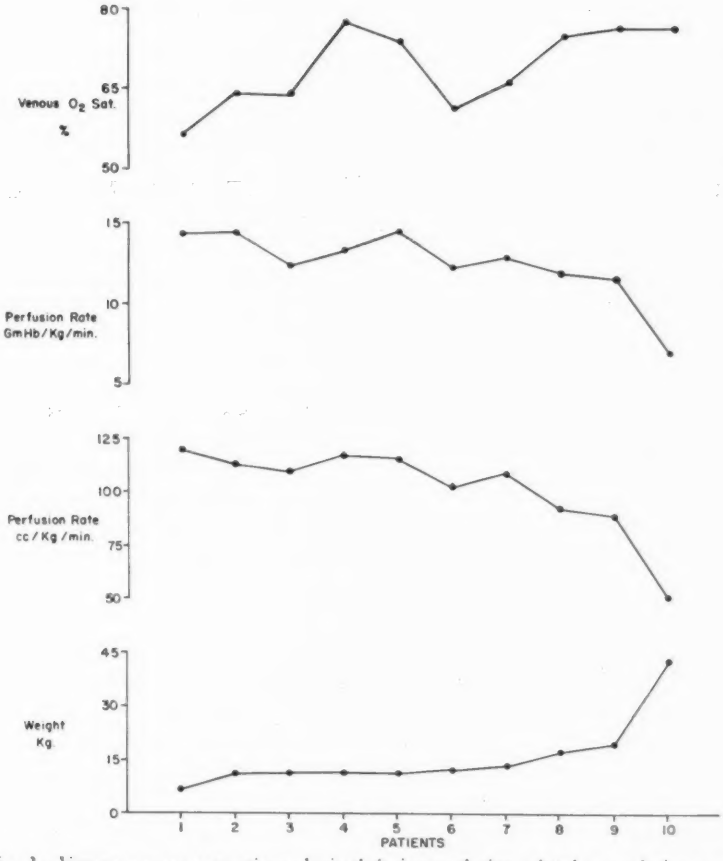


Fig. 2.—Venous oxygen saturations obtained during perfusion related to perfusion rate and weight of the patient.

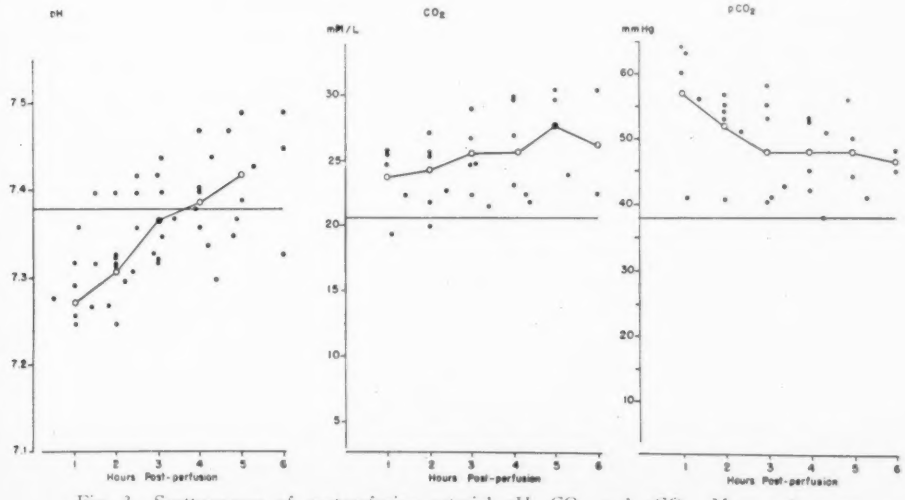


Fig. 3.—Scattergrams of postperfusion arterial pH, $CO_2$, and $pCO_2$. Mean values are plotted. The abscissae represent hours from the time the pump was turned off.

state. The pH of the venous blood varied between 7.26 and 7.44, with a mean value of 7.35. The carbon dioxide content varied between 15.1 and 23.5 mM/L. The arterial oxygen tension ranged from 500 to 550 mm. Hg and the arterial pH from 7.33 to 7.45.

In the postperfusion period, a more or less constant pattern for all patients appeared from the intermittent arterial sampling (Fig. 3). Initial pH values were usually low, the lowest being 7.25, but showed a steady rise, so that most were normal by three hours and all were within the range of normal by six hours. The $CO_2$ contents initially were elevated and remained so during the sampling period. The $pCO_2$ likewise was initially elevated but showed a tendency to fall during the sampling period. The over-all picture is one of mild respiratory acidosis.

The postperfusion arterial oxygen tensions were of note because of the low values obtained (Fig. 4). While relatively high tensions could be achieved in patients being manually ventilated with 100% oxygen, in patients spontaneously breathing room air, or in those in whom some complication, such as a temporary pneumothorax occurred, arterial oxygen tensions ranged from 29 to 77 mm. Hg. When 100% oxygen was administered via a catheter in a tracheotomy tube, values for arterial oxygen tension ranged from 75 to 165 mm. Hg, with a mean of 102 mm. Hg. By comparison, anesthetized dogs not operated upon and ventilated in a comparable fashion achieve arterial oxygen tensions ranging

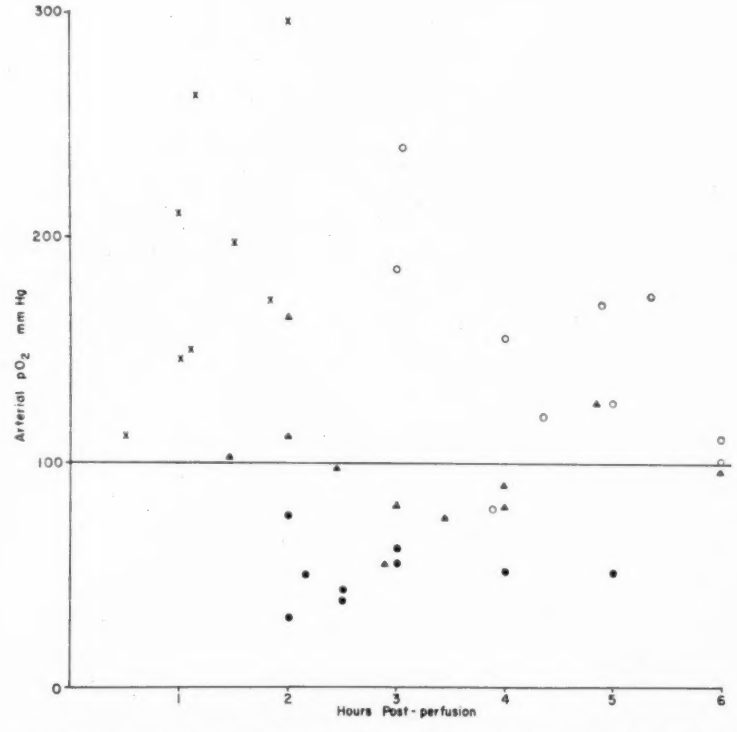


Fig. 4.—Postperfusion arterial oxygen tensions. Crosses indicate ventilation assisted with 100% oxygen; solid circles, room air breathed or association with mechanical interference with respiration; triangles, spontaneous respirations, 100% oxygen administered via a tracheotomy tube; clear circles, spontaneous respirations in oxygen tent.

from 160 to 280 mm. Hg, with a mean value of 210 mm. Hg. With one exception, patients breathing unassisted in an oxygen tent had values for arterial oxygen tension in excess of 100 mm. Hg. These latter samples were obtained toward the end of the sampling period, when the patient had reacted from anesthesia.

All patients survived the operative procedure. One of the patients died six weeks postoperatively of a cause unrelated to the perfusion.

## Comment

Other investigators using, in general, lower perfusion rates have reported metabolic acidosis either occurring shortly after perfusion [6,7] or having its onset three or more hours postoperatively.[8] The data from this study indicate that if patients are perfused with fully oxygenated blood of normal pH at a rate which yields venous oxygen saturations in excess of 50%, metabolic acidosis does not occur. Furthermore, there is no need to perfuse at alkaline pH's in anticipation of ensuing metabolic acidosis or to administer alkali in the postoperative period.

The postperfusion respiratory acidosis and low arterial oxygen tension point to reduced pulmonary efficiency in these patients; however, this is not a condition unique to the perfused patient. Other investigators [9,10] have reported comparable acidosis occurring during and after thoracotomy for procedures not involving perfusion. This is not to imply, however, that these perfused patients routinely have benign and uncomplicated postoperative courses, such as is now expected in patients undergoing cardiac surgery in which perfusion is not involved. Respiratory problems, including atelectasis and excessive secretions in the tracheobronchial tree, have been common and troublesome postoperative complications.

Recently Ito, Kolff, and Effler [11] and Kirklin [12] have suggested that some deaths occurring 10 to 12 hours following perfusions might be the result of oxygen toxicity produced by perfusing patients with blood of high oxygen tension. We have consistently perfused both patients and dogs at oxygen tensions ranging between 500 and 550 mm. Hg without producing detectable evidence of oxygen toxicity. It is perhaps pertinent to note that patients undergoing various other forms of surgery are frequently ventilated with gas mixtures containing oxygen in a sufficiently high percentage to yield arterial oxygen tension in excess of 500 mm. Hg, and evidence of oxygen toxicity has not been seen in these patients. Since the solubility of oxygen in blood is decreased with increasing temperatures, a potential hazard of producing oxygen bubbles in the patient's arterial system exists if blood of high oxygen tension is pumped into the patient at less than body temperature. This hazard is obviated if the blood in the machine is maintained at the temperature of the patient's blood.

## Summary and Conclusions

Patients perfused with fully oxygenated blood of normal pH at a rate which yields venous oxygen saturations in excess of 50% do not develop metabolic acidosis in the postoperative period.

Postoperative respiratory acidosis, comparable to that reported in patients undergoing thoracotomy for procedures not involving perfusion, may occur but is mild and of short duration.

Sudden postoperative deaths, ascribed by some to oxygen toxicity, have not occurred in these or other patients who perfused at arterial oxygen tensions in excess of 500 mm. Hg.

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# Prevention of Fibrillation During Hypothermia by Pericardial Space Perfusion

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The two greatest deterrents to a more general acceptance of hypothermia as a clinical modality have been (1) the fear of ventricular fibrillation[1,2] and (2) the fear that hypothermia and rewarming will result in profound pathologic[3-5] and metabolic[6-8] changes which are difficult to correct or are irreversible. It has been felt by us that if, in spite of the control of fibrillation, the latter anxiety is justified, then serious consideration to the abandonment of clinical hypothermia is warranted.

A systematic evaluation of the effects of short and prolonged body cooling followed by rewarming has been made during the last three years by this laboratory. Information concerning the liver,[9] cardiovascular systems,[10,11] general pathology and histochemistry,[12] and various metabolic parameters[13-15] has been reported. From these experimental findings and a critical evaluation of the literature it is believed that there is no conclusive evidence to suggest that four to six hours of hypothermia as low as 23-24 C (73.4-75.2 F) and/or rewarming are attended with changes that would make one seriously consider eliminating its clinical use if the dangers of fibrillation could be avoided.

To our knowledge, no report related to intracardiac surgery under hypothermia has been free of regard for this arrhythmia, and, in general, it is conceded that it is preferable to prevent rather than treat it,[16] although good results with elective fibrillation have been described.[17,18] Since 1954, no less than 18 publications have presented clinical and experimental experiences with a variety of methods, mostly pharmacologic, concerned with the elimination of this hazard of hypothermia. Some of the agents or techniques reported are listed in Table 1. Their worth has varied from affording no protection, as with diphenylhydantoin (Dilantin), procainamide, Dacorene [2-(2-biphenylyloxy)-triethylamine],[25] and chlorpromazine,[22] to total prevention of fibrillation by procaine blockade of the sino-auricular node, as advocated by Riberi et al.[29] and Radigan and his co-workers.[30]

TABLE 1.—*Pharmacologic Agents and Other Techniques Evaluated for Their Antifibrillatory Effects During Hypothermia*

1. Acetylcholine [19,20]
2. Neostigmine (Prostigmin) [19,21,22]
3. Procainamide hydrochloride (Pronestyl) [22-24]
4. Bethanechol (Urecholine) chloride [24]
5. 2-diethylaminoethylisonicotinamide (Ambonestyl) [24,25]
6. Aminoacetic acid (glycine 5%) [22]
7. Diphenylhydaniton (Dilantin) sodium [24]
8. Dacorene [25]
9. Trimethaphen (Arfonad) [25,26]
10. Procaine or lidocaine (Xylocaine) infiltration of superior atriocaval junction [26-28]
11. Procaine (1%) I. V. or intrapericardially [29]
12. Chlorpromazine [22]
13. Quinidine [21,25]
14. Somatotropin [24]
15. Hyperventilation [3]
16. $CO_2$ with inspired oxygen [24]
17. Vagal nerve stimulation [18,28]
18. Sympathetic denervation of heart [25,28]
19. Vagotomy [28]
20. Cardiac denervation [28]
21. Coronary perfusion [24,25]
22. Cold acclimatization [20]

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John and Mary Markle Scholar (Dr. Fisher).

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The impracticability for clinical use of some methods, such as vagotomy[28] and cold acclimatization,[37] is obvious; the value of others, such as somatotropin,[33] must be confirmed, and with still others[2,34] there is a frank difference of opinion as to their value. Personal experience with many of these—both experimental (B. F.) and clinical (A. K.)—has not been gratifying.

The use of potassium for elective cardiac arrest, as proposed by Melrose et al.,[37] should be a valuable adjunct to the use of hypothermia in open cardiac surgery. However, in this laboratory, as in others,[16,38,39] when it was used in conjunction with lowered body temperature, difficulty in the restoration of normal cardiac rhythm was encountered.

The purpose of this paper is to report a method which has been effective in eliminating the incidence of fibrillation during experimental cardiotomy with total venous inflow occlusion and hypothermia, and which has permitted resuscitation of the potassium-stopped heart during general hypothermia.

## Methods

Seventy healthy mongrel dogs of both sexes, averaging 10 kg. in weight, on the standard laboratory diet of Purina, were used in this study. Food, but not water, was withheld for 12 hours prior to the induction of hypothermia. All animals were lightly anesthetized with open-drop ether and, as is customary for all hypothermia experiments in this laboratory,[14] were immersed in a 4 C water bath, where they remained until body temperatures, as determined by a thermocouple inserted well into the rectum (Tele-Thermometer *), reached 29 C. Upon removal from the bath they were dried and placed in a thermostatically controlled air-conditioned room, and body temperatures were permitted to drop to 24-26 C. A polyethylene catheter for blood pressure determinations was inserted into the femoral artery. Blood pressures were transmitted by a Hathaway strain-gauge and transcribed on a multichannel Sanborn recorder, as were EKG tracings (Lead II). Another catheter was introduced via the external jugular vein into the superior vena cava for the withdrawal of blood samples and the administration of fluid.

Fig. 1.—Technique of pericardial-space perfusion.

Animals were placed at random in one of five groups. In Groups I and II, control hypothermia and pericardial-space perfusion respectively, right thoracotomy was performed. Groups III, IV, and V, subjected to potassium arrest, had a bilateral thoracotomy to facilitate the clamping of the aorta and injection of the potassium citrate. Just prior to thoracotomy all animals were placed on a positive-pressure, automatic room-air respirator,† where they remained until, after rewarming, they could breathe spontaneously. Tapes were placed around the superior and inferior venae cavae for inflow occlusion, and intracardiac temperatures were recorded via a thermocouple inserted through the azygos vein into the right side of the heart. When animals were to undergo pericardial perfusion, two purse-string sutures of 00000 silk were placed at different levels of the anterior surface of the pericardium, and, through small openings made in the center of each, soft, flexible polyethylene catheters No. 14 were inserted into the pericardial sac and the purse-string suture drawn tightly around them (Fig. 1). One catheter was attached to the warm saline inflow bottle and the other to a receptacle at the side of the operating table. By interposing a coil of tubing submerged in a Dewar vacuum flask containing hot water, it was possible to assure a constant temperature of 40-44 C for the saline going into the pericardial

* Yellow Springs Instrument Co., Yellow Springs, Ohio.

† Medtronic Instruments, Minneapolis.

catheter. Perfusion was continued until a differential temperature of 6 or 7 degrees (C) was established between the rectal and the intracardiac temperature or the rectal temperature was seen to rise, which usually occurred when such a differential was established. To accomplish this, an average of 500 ml. of saline perfused in five to seven minutes was necessary.

All animals in all groups were subjected to venous inflow occlusion and cardiotomy, either atriotomy or ventriculotomy. When an atriotomy was done, a piece of atrium, as the object of another study to be subsequently reported, was removed.

Cardioplegia was accomplished in Groups III, IV, and V by injection of a 2.5% solution of potassium citrate containing 10 mg. of heparin into the ascending aorta after a vascular clamp was placed 2 cm. above the ostia of the coronary vessels. Digitalis was given intravenously, 0.02 mg/kg., to all animals in Groups IV and V one hour before cardiotomy. Venous inflow was reestablished by first releasing the superior vena cava and, after one minute, the inferior vena cava. In animals in which pericardial perfusion was performed prior to cardiotomy the heart was bathed with warm saline simultaneously with release of the occluding tapes. When fibrillation occurred, electric shocks, 100 volts, in rapid succession, were applied through saline-moistened padded electrodes.

Blood pH was obtained at room temperature using a Beckman pH meter just prior to venous inflow occlusion and just after release of the clamps. Serum potassium was determined at the same time, using a Coleman flame photometer. When the blood pH following release of the clamps was below 7.25, 15 ml. of 85% sodium lactate solution U. S. P., in the form of racemic sodium lactate, was administered. No other pharmacologic agents were used.

Following closure of the chest, animals were warmed in a 40 C water bath, and when the body temperature was 33-35 C, they were dried and returned to their cages. They remained under continued observation, and complete autopsies were performed on those that died. Animals considered permanent survivors lived at least several weeks.

To estimate the effect of pericardial-space perfusion upon cardiac output, this value was determined by the Evans blue dye technique [40] just prior to and after 10-15 minutes of perfusion. Cardiac index was obtained following determination of the surface area of the animals.

Data were subjected to statistical analyses utilizing Fisher's *t*-test.[41] A $P$ value of $<0.01$ was considered significant when comparing any two groups.

## Results

General information concerning the 70 animals in the five groups is summarized in Table 2. Values for blood pH and serum potassium just before venous inflow occlusion and just after the release of the clamps are presented in Table 3.

GROUP I: *Hypothermic Controls.*—Twelve animals were cooled to 25 C and subjected to thoracotomy. No significant difference in temperature between the rectum and the right atrium was encountered. In six animals a right ventriculotomy was performed, and all promptly fibrillated. Fibrillation ensued at one, one and one-half, two, two, four, and five minutes after ap-

TABLE 2.—*Summary of Seventy Animals Subjected to Hypothermia and Cardiotomy*

| Group No. | No. of Dogs | Temp. During Occlusion, Degrees (C) | | Length of Occlusion, Min. | No. Fibrillated | No. Defibrillated | Time to Restore Normal Rhythm, Min. | Survivals | |
|---|---|---|---|---|---|---|---|---|---|
| | | Rectal | Heart | | | | | No. | % |
| | | | | Hypothermic Controls | | | | | |
| I | 12 | 25 | 25 | 10 (7–11) | 10 | 1 | -- | 3 | 25 |
| | | | | Perfusion | | | | | |
| II | 20 | 25 | 31 | 10 (8–12) | 0 | -- | -- | 17 | 85 |
| | | | | Perfusion+K⁺Arrest | | | | | |
| III | 12 | 25 | 31 | 11 (8–13) | 4 | 3 | 9.2 (6–15) | 4 | 32 |
| | | | | Perfusion+Digitalis+K⁺Arrest | | | | | |
| IV | 19 | 25 | 31 | 13 (7–20) | 3 | 3 | 3.7 (0–11) | 11 | 58 |
| | | | | Digitalis+K⁺Arrest | | | | | |
| V | 7 | 25 | 25 | 12 | 3 | 3 | 9.0 (8–11) | 2 | 29 |

TABLE 3.—*Blood pH and Serum K in Dogs Subjected to Hypothermia and Cardiotomy*

| Group No. | Blood pH Venous Occlusion | | Serum K (mEq/L.) Venous Occlusion | |
|---|---|---|---|---|
| | Before | After | Before | After |
| I | 7.61 | 7.46 | 3.1 | 3.2 |
| | ±0.05 * | ±0.26 | ±0.6 | ±0.4 |
| II | 7.61 | 7.49 | 2.8 | 3.2 |
| | ±0.19 | ±0.67 | ±0.4 | ±0.7 |
| III | 7.66 | 7.49 | 2.8 | 4.5 |
| | ±0.18 | ±0.13 | ±0.4 | ±1.3 |
| IV | 7.52 | 7.39 | 3.1 | 4.5 |
| | ±0.15 | ±0.14 | ±0.5 | ±1.9 |
| V | 7.62 | 7.38 | 2.6 | 4.1 |
| | ±0.11 | ±0.07 | ±0.1 | ±0.1 |

* Standard deviation.

plication of the venous inflow clamps. In spite of diligent cardiac massage and repeated electric shock for a protracted period of time, none of the hearts could be made to resume a normal rhythm. Right atriotomy was done on six additional animals. Four of the six began to fibrillate at 30 seconds and 7, 8, and 9 minutes after cessation of circulation. One was readily defibrillated and permanently survived. The other three, just as with those subjected to ventriculotomy, could not be restored to normal rhythm. Two dogs with venous occlusion for 10 minutes did not fibrillate, but maintained a regular beat throughout and were also permanent survivors. Thus, 3 of 12 dogs, or 25%, recovered. Blood pH ranged between 7.57 and 7.90 just before venous clamping and 7.20 to 7.80 after release of the clamps. One animal, with a pH of 7.20 upon release of clamps, was given sodium lactate solution. Serum potassiums were between 2.3 and 3.8 mEq/L. prior to occlusion and 2.8 and 4.0 mEq/L. after occlusion. No statistically significant difference existed either for pH or potassium before or after release of venous inflow clamps.

GROUP II: *Pericardial Sac Perfusion.*—In this group of 20 dogs, perfusion of warm saline through the pericardial sac was maintained until a 6 to 7 degree (C) temperature differential between the right atrium and the rectum was obtained. This was readily accomplished. In four animals upon which brain temperatures were recorded during perfusion no increase in this temperature was noted in any instance, it remaining similar to the rectal temperature. Venous inflow occlusion clamps were applied just prior to cessation of perfusion. The average length of occlusion was 10±1.3 minutes. In 12 dogs right ventriculotomy was performed, and 8 were subjected to a right atriotomy with removal of a segment of atrial myocardium. Fibrillation was not encountered in a single instance, before, during, or after occlusion. With the begin-

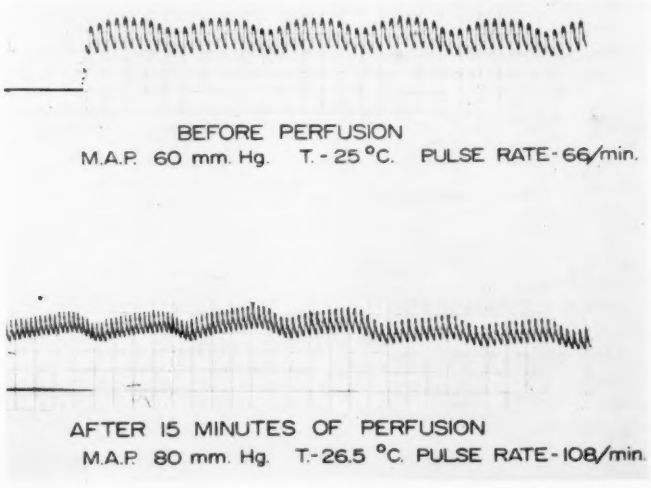


Fig. 2.—Effect of pericardial-space perfusion upon arterial blood pressure.

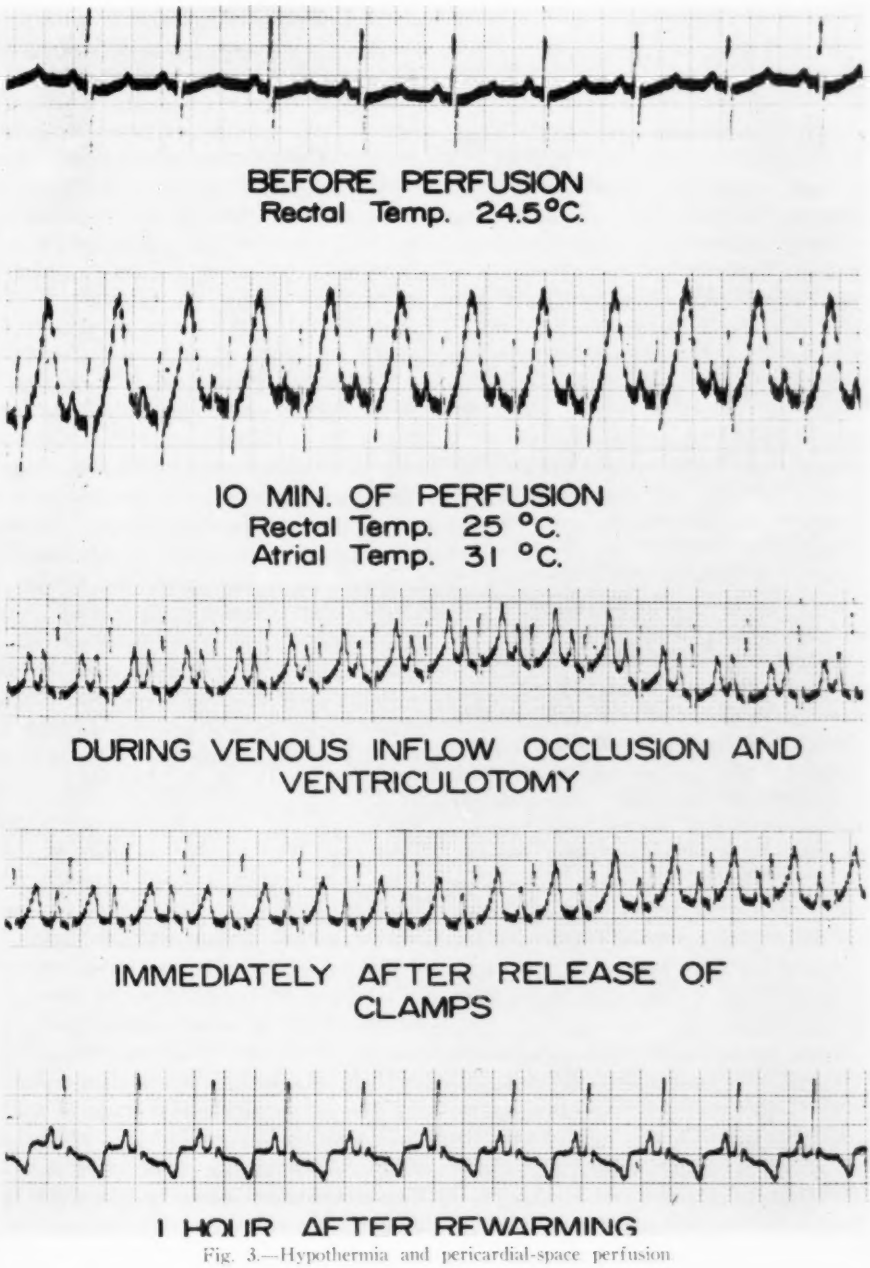
BEFORE PERFUSION
Rectal Temp. 24.5°C.
10 MIN. OF PERFUSION
Rectal Temp. 25 °C.
Atrial Temp. 31 °C.
DURING VENOUS INFLOW OCCLUSION AND VENTRICULOTOMY
IMMEDIATELY AFTER RELEASE OF CLAMPS
1 HOUR AFTER REWARMING

Fig. 3.—Hypothermia and pericardial-space perfusion.

ning of perfusion there was a prompt increase in the vigor of the cardiac contraction and a perceptible increase in pulse rate. As shown in Figure 2, a gradual elevation of venous-arterial blood pressure (15-20 mm. Hg) was observed in most animals.

Effect of perfusion upon cardiac output was determined in five dogs. Just prior to its onset, the cardiac index was 1.7±0.3 L/min/sq. m. This figure is similar to that previously reported [11] for dogs at this temperature. Following 10 to 15 minutes of contact of the heart with warm saline, the mean value was 2.6±1.2 L/min/sq. m. In three of the five dogs the cardiac index was increased by 100%. One animal showed no change, and in one there was slight decrease. Electrocardiographic changes due to perfusion were fairly constant and are typified in Figure 3. An increase in voltage occurs, with an overshooting and widening of the base of the T-waves. P-waves are peaked. The changes in the T-waves are more pronounced with the speed of the perfusion. These changes appear with the myocardial temperature change and are absent upon rewarming. Blood pH and serum potassium before and after clamping demonstrated no statistically significant difference and were similar to those in Group I. All of the animals but three made a totally uneventful recovery, survived permanently, and appeared to be normal in all respects. One animal died 12 hours after rewarming with a massive atelectasis; one was found dead the next day with a hemothorax, and one succumbed three hours after rewarming for no apparent reason. Two of the three had atriotomies.

During the period of caval occlusion the heart beat was regular and forceful. Although clamps were removed after as long as 12 minutes, this was not because the heart appeared cyanotic or showed evidence of difficulty.

Group III: *Perfusion and Potassium Arrest.*—Encouraged by the good results with pericardial-space perfusion, it was felt that if the heart could be stopped the occlusion time could be prolonged without producing any deleterious effect upon it, or, even if the time was not extended, at least the quiet heart would permit greater operating facility during the time available. Further, it was felt that perhaps the warm heart could be restored to normal rhythm after potassium cardioplegia more easily than is generally possible when it is hypothermic. Thus, utilizing perfusion of the pericardial sac with warm saline, a temperature differential of 6 degrees (C) was established in animals similar to that in Group II. Of the 12 animals in this group, none fibrillated during perfusion or prior to cardioplegia. An average of 10.8 ml. of 2.5% potassium citrate solution containing heparin was required to produce complete arrest, as indicated electrocardiographically. Right ventriculotomy was performed in six animals and right atriotomy in six. Venous occlusion time averaged 11 minutes, the longest being 13 and the shortest 8 minutes. Upon release of clamps, institution of cardiac massage, and the dripping of warm saline over the surface, the hearts of eight animals were seen to return to normal rhythm after several minutes, only to be followed by subsequent fibrillation in four. In three the rhythm readily reverted to normal, but one could not be defibrillated. Four dogs failed to show evidence of electrical activity after protracted massage and flooding of the chest with warm saline. Permanent normal rhythm was established in 7 of the 12 dogs after an average time of 9.2 minutes following release of the caval clamps. Four of these animals were permanent survivors. The other three died one-half, one, and six hours after rewarming, and autopsy disclosed no cause of death. No animal in this group had a pH below 7.34 following release of the inflow clamps. Consequently, no animal in this series received sodium lactate. Subsequent to the release of the clamps and the beginning of cardiac massage there was an increase in serum potassium as it was being "washed

out" of the heart. All of the four animals that survived had atriotomies.

Thus, in spite of the pericardial-space perfusion, difficulty was encountered in restoration of the heart beat following cardioplegia. However, three of four animals fibrillating subsequent to restoration of normal rhythm were easily defibrillated.

GROUP IV: *Digitalis and Perfusion with Potassium Arrest.*—Because most of the animals in Group III died after restoration of normal rhythm from what seemed to be cardiac failure, and partially on an empiric basis, all animals in this group were digitalized prior to hypothermia and pericardial perfusion. Once again, no animal in this group was seen to fibrillate prior to cardioplegia. With the release of clamps and institution of massage, permanent, normal rhythm in the 19 animals was restored within an average time of 3.7 minutes. Three animals fibrillated subsequent to immediate restoration of a normal heart beat, but they were all rapidly and easily defibrillated. Encouraged by the ease of restoration of the heart beat and the increased number of permanent survivors over that found in Groups II and III with comparable periods of occlusion, circulatory arrest was prolonged for as long as 20 minutes. Included with the 11 permanent survivors are animals whose venae cavae were clamped for 15, 17, and 20 minutes. Of the eight not surviving permanently, two died 2 days after recovery, three 1 day after recovery, and three within 12 hours after rewarming. Included in this last group are animals with circulatory arrest for 14, 15, and 18 minutes. One of the deaths was due to a massive atelectasis. As in the other groups, no statistically significant difference for pH before and after venous occlusion was encountered. In two animals (pH, 7.15, 7.18), sodium lactate was administered intravenously. As in Group III, a slight elevation of serum potassium was found after release of clamps. The average amount of potassium necessary to induce cardioplegia was practically identical with that in Group III. In this group, 10.6 ml. (2.6 mEq.) was administered. Electrocardiographic changes were typical of those demonstrated in Figure 4. The changes noted with perfusion alone were observed, except that the heart rate was not as rapid. The same return toward normal of the T-wave after rewarming, as observed in Figure 3, was seen.

GROUP V: *Digitalis and Potassium Arrest.*—Because of the better results when animals were digitalized prior to pericardial-space perfusion and potassium cardioplegia, it was considered worth while to determine whether digitalis had any beneficial effect on recoverability in cardiac-arrested animals in which hearts were not warmed. All seven dogs in this group were subjected to venous occlusion of 12 minutes while at 25 C. Upon release of the inflow clamps and the beginning of massage, three animals fibrillated. In all normal rhythm was restored with difficulty. An average time of 9 minutes (8-11 minutes) was necessary to restore a permanent regular heart beat. Five of the seven dogs died within 12 hours after rewarming, and two were permanent survivors. In no instance was the blood pH found to be below 7.40 (range, 7.40-7.55) after release of clamps. The slight increase in serum potassium previously noted in potassium-arrested hearts was observed.

## Comment

The value of hypothermia and the use of preventive measures to avoid fibrillation have long been debated. The various methods employed are one more exponent of human ingenuity. But the fact remains that results have been controversial and the conclusions discordant.

Pericardial-space perfusion has resulted in a significant diminution of ventricular fibrillation with a distinct decrease in mortality rate. With this technique, the advantages offered by a general state of body hypothermia prevail, and, at the same time, the temperature of the myocardium approx-

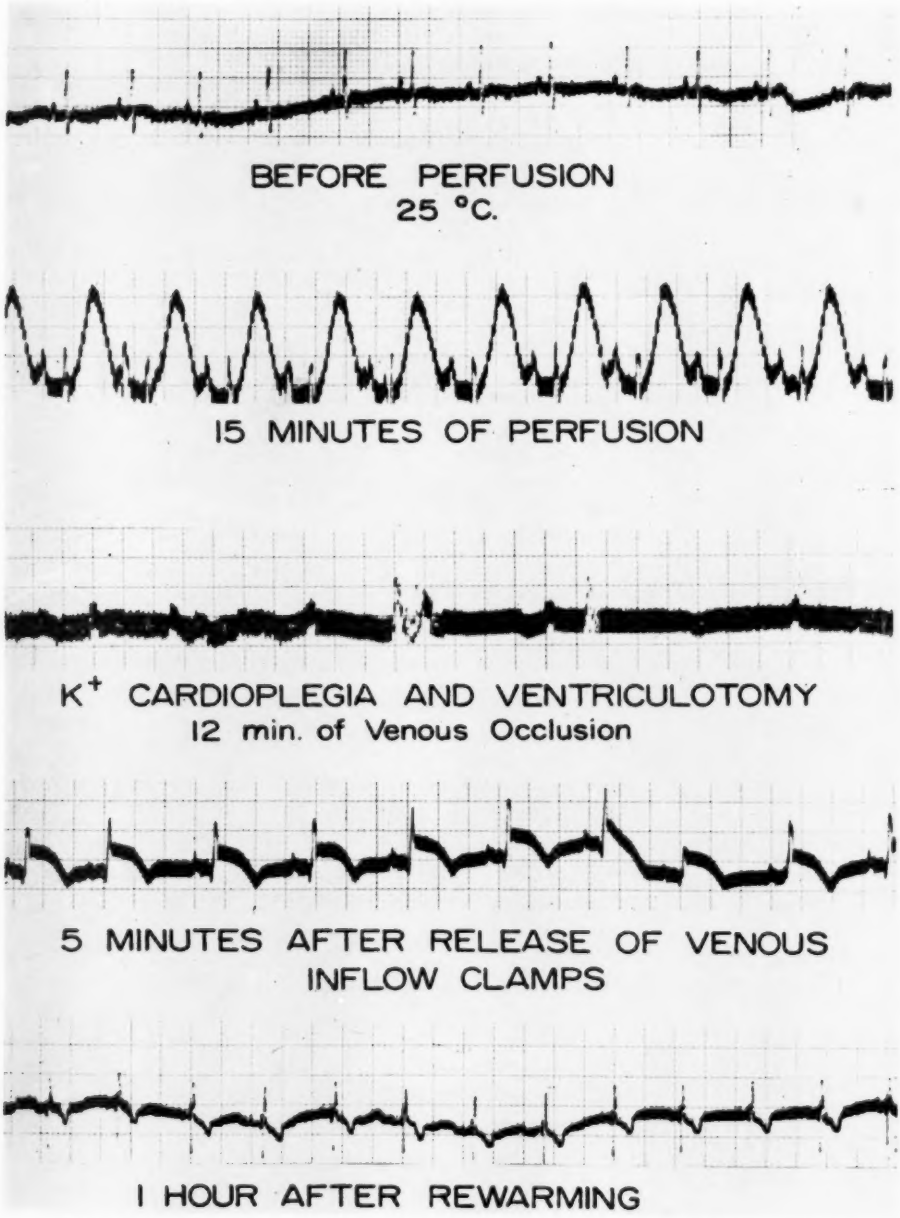


Fig. 4.—Hypothermia and pericardial-space perfusion with digitalis and $K^+$ cardioplegia.

imates normal, so that its irritability is diminished.

In spite of the many theories advanced to explain cardiac irritability during hypothermia, it is still our opinion that temperature itself is of prime importance.[9] The failure to correlate blood pH or serum potassium levels with the occurrence of fibrillation is repetitious of earlier findings.[9]

The impression gained upon looking at the heart during pericardial perfusion, that there are an increase in cardiac activity, stronger contraction, and improved color of the myocardium, is objectively demonstrated by the tachycardia, increase in blood pressure, and cardiac output that occurs. The actual value of bradycardia during hypothermia is still debatable and would seem to be different from that induced by stimulation of the vagus nerve at normal temperature.[42] In the latter, there is an increase of the total cardiac cycle by over 300%, but the duration of systole increases by only 50%. Thus, the resting period is prolonged. During hypothermia there is a similar increase in the time of the total cycle, but the duration of both systolic and isometric relaxation increases by 250%. Thus, by accelerating the heart rate through perfusion, no alteration of a situation which is totally beneficial is accomplished. Further, the tachycardia induced is accompanied, for the most part, by an increase in cardiac output and blood pressure. That this results in improved coronary and systemic circulation might well be expected. Likewise, their elevation would afford proof that pericardial perfusion does not interfere with venous return and proper filling of the heart.

The consistent electrocardiographic finding of a marked elevation of the T-wave, which changes in shape and size according to the speed of the perfusion, would seem to be innocuous, for it became entirely reversed to a normal configuration once the perfusion was stopped. That drops of warm and cold saline on the myocardium could bring about changes in the electrocardiogram was demonstrated by Prinzmetal.[43] In 1921 Eyster and Meek[44] found that cooling of the sinoatrial node depressed its activity, and that pacemaker action was picked up by the areas of the myocardium where the temperature was lower. Further, they observed that localized heating of the myocardium, other than the sinus, would establish an ectopic pacemaker. Experiments reported here demonstrated that the bathing of the heart with a uniform transmission, gradient, and heat loss resulted in a different effect.

The difficulty encountered in the restoration of the potassium-arrested heart to permanent, regular rhythm and the high mortality, even after reestablishment of a normal heart beat, probably due to ineffective ventricular contraction, have been described by others in both the normothermic and the hypothermic animal. Pericardial-space perfusion did not alter this. However, animals fibrillating were more easily defibrillated. With the preliminary digitalization of animals subsequently subjected to potassium cardiac arrest following pericardial perfusion, a marked improvement in results was noted. Normal rhythm was more rapidly accomplished and mortality was lessened. Although body and heart temperatures, lengths of occlusion, and all other factors were similar, the group subjected to cardioplegia had a smaller per cent of permanent survivors than did those in which the heart was permitted to beat during circulatory arrest. The mechanism of the beneficial effect of digitalis in combination with pericardial perfusion is obscure and is in the process of investigation. Results with digitalis in cardiac-arrested animals that were hypothermic and without pericardial perfusion were no better or worse than when pericardial perfusion without digitalis was used in such animals.

No attempt was made in this study to explore the absolute length of time of safe occlusion or the limit to which temperature could be lowered. These parameters would seem worth defining.

Further, it is not intended that this technique in any way be substituted for existing procedures, i. e., coronary perfusion or extracorporeal circulation. It is recognized that the time permissible for circulatory occlusion is limited, but if our diagnostic acumen could reach the stage where we could anticipate with reasonable certainty that cardiotomy of 10, 12, or 14 minutes would be ample, then this technique would seem to have clinical merit. It is likely that its greatest value would be its use in conjunction with coronary perfusion and/or hypothermia with a low-flow extracorporeal system.

## Summary and Conclusion

Experimental evidence would suggest that moderate hypothermia of up to several hours is not attended with deleterious effects that would demand its abandonment for clinical use if the danger of fibrillation could be avoided. A simple technique of differentially warming the heart by pericardial-space perfusion has been highly successful in eliminating this complication during circulatory arrest and cardiotomy.

In conjunction with predigitalization, this technique has permitted the prompt restoration of normal cardiac rhythm following potassium-induced cardioplegia. However, it has been observed that the incidence of permanent survival is reduced in animals by cardiac arrest during a period of venous inflow occlusion, readily tolerated if the heart is permitted to beat. Survivors in these experiments include animals with venous inflow occlusion of 15-20 minutes' duration.

Under these experimental conditions, within a wide range blood pH and serum potassium were not related to the onset of fibrillation, suggesting that temperature, or factors not yet elucidated, play a dominant role in the production of this arrhythmia.

This procedure is presented not as a better substitute for existing techniques but as an ancillary method for permitting the use of hypothermia with greater safety.

Mr. Wayne Foster gave technical assistance in this project.

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## DISCUSSION

DR. JOHANN L. EHRENHAFT, Iowa City: I realize that hypothermia is not the most fashionable thing to talk about these days, but we feel that the method is still an excellent and simple one in the treatment of certain types of intracardiac defects. We still advocate hypothermia technique and open cardiotomy in all cases of cardiac lesions which can be repaired by this simple method and in which the use of the extracorporeal circuit is not necessary.

Our total clinical experience with hypothermia is about 110 cases. Of these 110 patients, slightly over 60 had correction of interatrial septal defects. Ventricular fibrillation occurred in 25 of those 60 patients. Restoration of sinus rhythm was accomplished in all but two who had severe pulmonary hypertension. We, as well as all others who have used this method, have learned that cooling below 30 C is not necessary. Most of the instances of ventricular fibrillation occurred in patients who were cooled below that level, usually to around 27 C, and in whom the inflow- and outflow-tract occlusion was prolonged.

We do not agree with the recent trend in surgical circles to condemn hypothermia technique, and we feel that we will continue the use of this method in well-selected patients who are suitable for treatment by this simple and effective means.

DR. WILIAM O. MCQUISTON, Peoria, Ill.: I think this paper may be quite a contribution to the use of safe hypothermia. I have two questions I should like to ask. One concerns the temperature of the perfusion solution. The other is whether the length of time that can be gained by a 25 C temperature is worth the danger involved at temperatures between 25 and 30 C.

DR. BERNARD FISHER, Pittsburgh: I should like to thank both discussants.

In answer to the questions: The saline perfused was between 40 and 44 C, and it took us six or seven minutes to establish the temperature differential by perfusing the saline.

As to whether the time gained by the 25 C temperature, is worth the danger, in our experience with several hundred animals in the laboratory, we have never had any real difficulty with fibrillation developing as the temperature was going down to 25 C, until we opened the chest and did what we showed here.

Concerning the question of how long the brain can be protected, we cannot answer that by this study. Incidentally, we measured brain temperatures to see whether warming the heart might result in a concomitant warming of the brain. It did not, the brain temperature falling exactly with the rectal temperature.

# Surgery for Congenital Coronary Artery Arteriovenous Fistulae

EGBERT H. FELL, M.D.; MILTON WEINBERG Jr., M.D.; ARCHER S. GORDON, M.D.; BENJAMIN M. GASUL, M.D., and FRANK R. JOHNSON, M.D., Chicago

Reports concerning the occurrence of anomalous coronary arteries entering directly into the venous system, such as the right ventricle, right atrium, coronary sinus, or pulmonary artery, are rare. The surgical correction in one patient with an anomalous left coronary artery entering the right ventricle was successfully accomplished in June, 1953, and reported by our group.[1] Three other cases are known to us that were successfully corrected surgically.[1,3,10,11] This unusual anomaly has been found during exploration for an intrathoracic arteriovenous fistula, but no attempt to repair the lesion has been documented, other than those referred to above.

In two of our four cases the condition was correctly diagnosed prior to surgery. The details of the diagnostic procedures will be reported by Dr. Benjamin M. Gasul and associates in another communication. In the first patient, an 18-year-old girl, the condition was diagnosed as a patent ductus arteriosus. In the second and fourth patients the defect was correctly diagnosed. The abnormal location of the machinery murmur stimulated great interest, followed by careful medical and cardiovascular physiological studies. The angiocardiograms and cardiac catheterizations clearly demonstrated the lesions and the degree of shunt into the right ventricle. The third patient's preoperative diagnosis was a rupture of the sinus of Valsalva into the right ventricle. The huge aneurysmal dilatation of the right coronary, as shown by the angiocardiogram,

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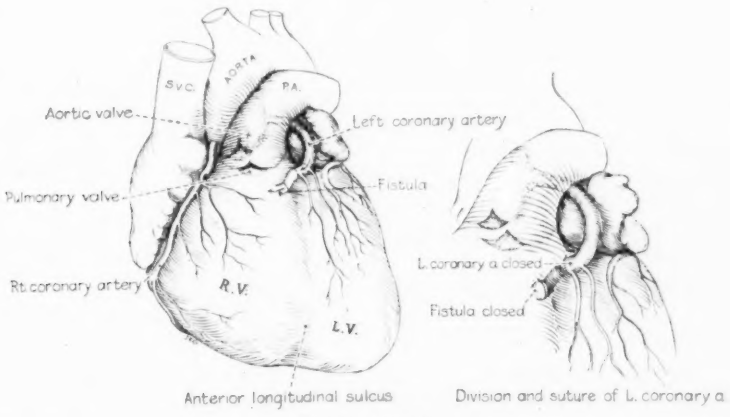


Fig. 1.—Case 1

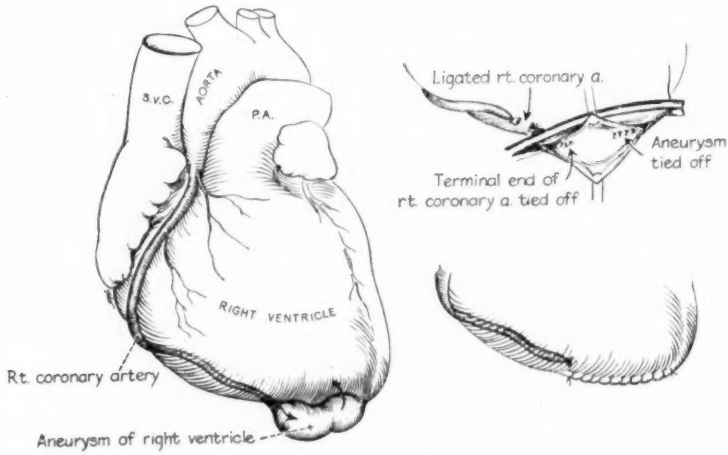


Fig. 2.—Case 2

with the large shunt into the right ventricle, led us to believe in this preoperative diagnosis.

Case 1.—This 18-year-old girl had a preoperative diagnosis of a patent ductus arteriosus. The heart was of normal size. At operation a ligamentum arteriosum was found and a thrill palpated on the outflow tract of the right ventricle (June, 1953).

The drawing on the left illustrates the anomalous left coronary artery, 6 mm. in diameter, entering the right ventricle just proximal to the pulmonary valve. The drawing on the right depicts the surgical correction. The terminal end of the anomalous vessel was freed from its epicardial bed, divided, and the ends sutured. Recovery was complete.

Case 2.—A 14-month-old boy had a machinery murmur at the cardiac apex. The preoperative diagnosis was anomalous right coronary artery with aneurysm of the right ventricle and arteriovenous fistula. The heart was moderately enlarged.

The drawing of the heart shows a large coronary artery following its normal course and entering an aneurysm at the apex of the right ventricle. The coronary artery was 5 mm. in diameter at its insertion into the aneurysm.

The drawing at the upper right shows the coronary artery tied and divided, the aneurysm opened and the ostia of the coronary artery and the ventricle sutured (March, 1957).

At the lower left the drawing shows the ventricular wall of the aneurysm sutured and the terminal end of the right coronary artery closed. The child made a complete recovery.

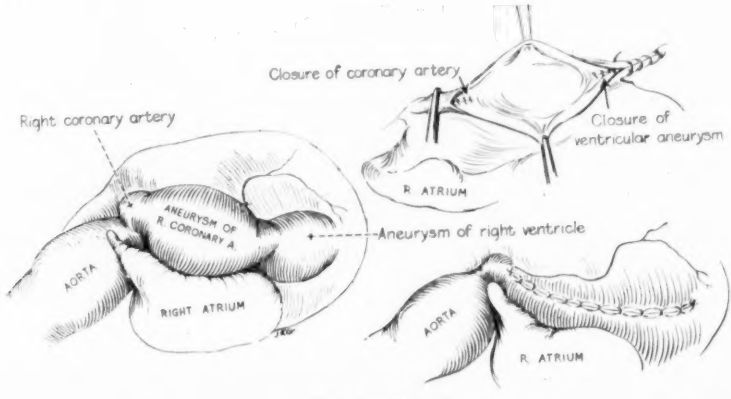


Fig. 3.—Case 3

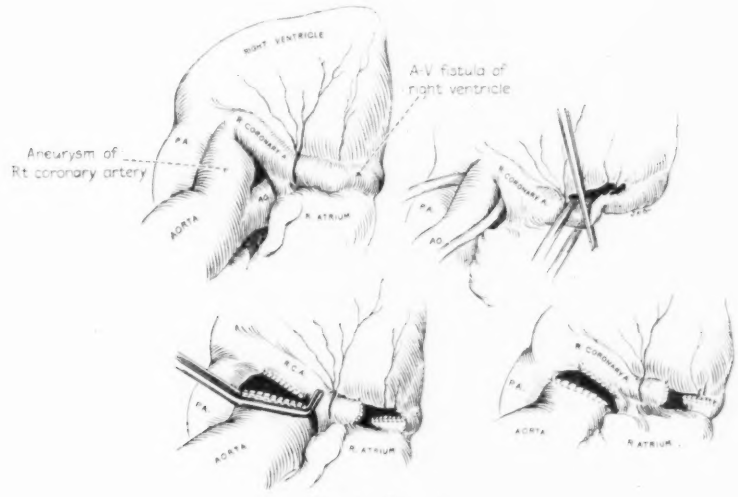


Fig. 4.—Case 4

CASE 3.—A boy 3 years of age had developed normally but was dyspneic on exertion. A machinery murmur was heard to the right of the sternum in the third, fourth, and fifth interspaces. The preoperative diagnosis was rupture of the sinus of Valsalva into the right ventricle. The heart was considerably enlarged. The drawing at the left was made from the head of the table to the right of the patient. The right coronary artery at its origin was 2+ cm. in diameter; the aneurysm of the right coronary artery was 6+ cm. in diameter and emptied into an aneurysm of the right ventricle. With the aid of the pump-oxygenator the aneurysm was opened, as seen in the upper right illustration. The opening, 2 cm. in length, into the right ventricle was sutured, and the coronary artery was closed near its origin. The edges of the sac were excised and the remainder sutured, as depicted in the lower right drawing (October, 1957). This patient has normal heart findings at the time of this report.

CASE 4.—This boy, aged 9½ years, had as the first diagnosis, four years ago, ruptured sinus of Valsalva into the right ventricle. He had cardiac enlargement with minor cardiac symptoms. A loud machinery murmur was present at the right of the sternum at the third and fourth interspaces. Recent angiocardiographic studies led to the diagnosis of an anomalous right coronary artery with a fistulous opening into the right ventricle.

The drawing at the upper left was made from the head of the table on the patient's right and shows the origin of the right coronary artery to be huge and aneurysmal in character, 3.5 cm. in diameter, followed by a large, rather tortuous artery, which emptied into an aneurysm of the right ventricle at the site of the fistula. A marked thrill was felt at this point (January, 1958).

The drawing at the upper right shows the origin of the coronary artery freed and a small rubber drain placed about it. The distal portion of the artery just before it enters the right ventricle has been freed and is being clamped and divided.

The drawing at the lower left shows the opening into the left ventricle sutured, the coronary artery just proximal to it also sutured, and the arteriovenous fistula thus closed. The right coronary artery at its origin has been divided and the ends sutured, eliminating the aneurysm.

The illustration at the lower right shows the completed surgical procedure. The patient is well, with normal cardiac function.

## Comment

Aneurysms of the coronary arteries may be either congenital or acquired. The diffuse aneurysm with an arteriovenous communication has been considered congenital in origin and most commonly found involving the right coronary artery. In this small series of four cases, the right coronary with a diffuse aneurysm communicated directly with the right ventricle in two of the cases (Figs. 3 and 4). The 14-month-old boy's large right coronary emptied into an aneurysm at the apex of the right ventricle (Fig. 2). The communication of the large

anomalous branch of the left coronary artery with the outflow tract of the right ventricle was not associated with an aneurysm of the artery or ventricle (Fig. 1). We believe these anomalies to be congenital.

The histories of the three boys (14 months to 9½ years) revealed cardiac murmurs heard as early as the ages of 1, 1½, and 7 months, respectively, and they were observed in the Cook County children's cardiac clinic from one month to three years prior to surgery. Development was normal in each patient. One (a 3-year-old child) was considered slightly undernourished. All showed cardiac enlargement, and a machinery murmur was heard at the apex or to the right of the sternum in each case. The catheterization studies revealed a left-to-right shunt into the right ventricle. Angiocardiograms and aortograms localized the lesions and were diagnostic in two cases and were believed to show a ruptured sinus of Valsalva in one case. The anomalous left coronary artery did not have angiocardiographic studies and was believed to be a patent ductus arteriosus prior to operation.

Aneurysms and arteriovenous fistulae throughout the body are hazardous. The presence of such lesions of a coronary artery, we believe, presents a very serious problem. Patients have been reported living 60, 70, and 87 years without cardiac difficulties, while others have died early in life, as a result of an infection at the site of the fistula, or rupture of the aneurysm, or both.

Our experience with these four cases leads us to believe that patients with a coronary artery arteriovenous fistula well tolerate closure of the fistula and excision of the aneurysms of the artery or ventricle or both. There has been no mortality, and all four patients now have normal cardiac function and no left-to-right shunt exists.

## Summary

Four patients, 14 months to 18 years of age, with anomalous coronary arteries communicating with the right ventricle, are briefly described. The right coronary artery was anomalous in three, and associated with aneurysms of the artery and right ventricle in two and with an aneurysm of the right ventricle in one. The anomalous left coronary artery was not associated with an aneurysm.

In two of the four patients the condition was correctly diagnosed prior to surgery.

Surgical correction was successful in each case; the fistulae were closed and the aneurysms resected. All have normal cardiac function at this time.

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## DISCUSSION

DR. ROBERT H. WHITTLESEY, Cleveland: I should like to cite two cases of aneurysm of the heart, neither of which were mine.

The first was reported by Dr. Willis Potts about 1953. Dr. McQuiston can confirm the date of the report. The patient was an 8- or 9-year-old white boy who had an aneurysm of the left ventricle that extended down through the diaphragm and presented through a rather large epigastric hernia. The EKG showed left axis deviation, and at operation, which was done without the use of a pump-oxygenator, the aneurysm was simply excised from the ventricle. Immediately, as the base of the aneurysm was clamped, the EKG returned to normal.

The second case occurred as I was senior resident with Dr. Potts, in 1954. This was of an aneurysm of the left auricle; the diagnosis was missed preoperatively. It was thought to be a tumor of the left chest, of some sort. (Both these lesions were approached through the fourth interspace in the left chest.) In this case, as the pleura was incised, the aneurysm was also incised. A clamp was quickly applied, and the aneurysm was simply excised, without difficulty. The patient made a good recovery.

DR. ORMOND JULIAN, Chicago: I congratulate Dr. Fell on the surgical technique, and the photographic technique as well.

One point that struck me as being tremendously interesting and explainable was the fact that he was unable to clamp the right coronary artery initially without producing a disturbance in coronary circulation, and then, later, after having repaired the drain-off into the right ventricle, he was able to do away with the right coronary artery entirely.

This situation is entirely analogous to that in any peripheral arteriovenous fistula—that is, if one divides the artery proximal to the fistula, the collateral circulation that is entering the artery within the area of the fistula or distally drains immediately into the lower-pressure venous area, and ischemia results.

The requirement in all arteriovenous fistulae of quadrilateral ligation and excision, which in effect Dr. Fell accomplished in this coronary fistula, is well recognized. I should think it would be fundamental to attack the drainage point first and then divide the coronary artery proximally, as he did.

DR. EGBERT H. FELL, Chicago: I wish to thank the discussants and to say that I was well cognizant of the aneurysms of the heart that Dr. Potts and others have seen and reported. We have had similar cases, but we have limited this paper to congenital anomalies of the coronary arteries with arteriovenous fistulae and aneurysms.

Dr. Julian's point is very well taken, and the case he referred to showed it to be valid.

Credit is due Dr. Benjamin M. Gasul and associates for the careful medical and cardiovascular physiological studies that concluded in correct diagnosis in two of the four cases. We believe that a correct preoperative or preautopsy diagnosis had not been made previously. The abnormal location of a machine murmur, a left-to-right shunt into the right heart, as demonstrated by catheterization, and a large, tortuous coronary artery shadow on the angiocardiogram, were present in three of the four cases. This triad is diagnostic.

# The Effect of an Intravenous Fat Emulsion on Liver Function

**JOANN M. GATES, M.D.; ANNE U. BARNES, M.D.; GEORGE C. HENEGAR, M.D., and FREDERICK W. PRESTON, M.D., Chicago**

Fat emulsions have been investigated extensively in an effort to find a safe source of calories for malnourished patients being maintained on parenteral feeding for prolonged periods. However, little attention has been paid to the effect of these emulsions on liver function. In view of the major role of the liver in intermediary fat metabolism and the frequent occurrence of accumulation of fat within the hepatic parenchyma, it seemed of interest to investigate the effects of repeated infusions of fat on the functions and structure of the liver.

## Methods

Daily infusions of 600 ml. of a fat emulsion were given to 20 hospitalized male patients. Ten patients had normal and 10 had abnormal liver function prior to the infusions, as judged by sulfobromophthalein U. S. P. (Bromsulphalein) retention. The patients were selected on the basis of their cooperativeness and their availability for biopsies and follow-up studies.

The fat emulsion (Lipomul-I. V.) contained 15% cottonseed oil, 4% dextrose, 1.2% soybean phosphatide, and 0.3% polyoxalkol (Pluronic F-68). The caloric content was 1.6 Cal. per gram. Each patient received 60 ml. of this emulsion daily.

TABLE 1.—*Liver Function Tests*

| | Normal Value |
|---|---|
| Sulfobromophthalein (Gaebler [7]) | 5% dye retention or less in 45 min. |
| Thymol turbidity (Shank & Hoagland modification of the Maclagan method [14]) | 5 units or less in 30 min. |
| Thymol flocculation (Neefe [13]) | Negative flocculation |
| Cephalin flocculation (Hanger [5]) | 2+ or less read at 48 hr. |
| Serum bilirubin (Malloy and Evelyn [12]) | 1.0 mg. total bilirubin per 100 ml. or less. |
| Urine bilirubin (2 hr. Watson method [15]) | 0.3 to 1.0 Ehrlich unit per 2 hr. |
| Serum protein (Kingsley [9]) | 6.5 to 8.0 gm. per 100 ml. |
| Serum glutamic oxalacetic transaminase (GOT) (Kaltenbach [8]) | 7 to 32 units per min. per ml. |
| Serum lactic dehydrogenase (LDH) (Kaltenbach [8]) | 7 to 32 units per min. per ml. |
| Blood prothrombin content (Quick one-stage method) | 70% to 100% |

Eighteen patients were given 14 consecutive infusions, and one each, 17 and 19 infusions. The time during which each infusion was administered varied from 0.75 to 5 hours, with an average of 2.2 hours. The infusions were well tolerated, and, although minor reactions occurred, they were not severe enough to warrant discontinuation of any infusions. The severest reaction attributable to the emulsion was a headache, which occurred daily for several hours in Patient 17 (Table 3) for the first eight days of the infusions.

The liver function tests listed in Table 1 were done before, during, and at intervals after the infusions.

Ten patients (Patients 1, 2, 5, 6, 7, 9, 10, 11, 12, and 19, Tables 2 and 3) had surgical operations prior to their courses of fat infusions. In each case preoperative liver function tests were obtained, and the infusions were not given postoperatively until the liver function had returned to its preoperative status as determined by retention of sulfobromophthalein.

Serum turbidity was determined daily on fasting specimens by means of per cent transmission of light in a Coleman Nepho-Colorimeter. The normal is 90% to 100% transmission. In each case the

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Miss Elizabeth Jane Jackson gave technical assistance, and Dr. Jeanne Cooper, Department of Pathology, Veterans' Administration Research Hospital, reviewed the microscopic sections.

TABLE 2.—*Liver Function Tests in Patients with Normal Sulfobromophthalein (Bromsulphalein) Retention Prior to Infusions*

| Patient | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, yr. | | 33 | 65 | 39 | 54 | 62 | 48 | 63 | 56 | 61 | 33 |
| Diagnosis | | Gastrojejunal ulcer | Hernia, leg ulcers | Peptic ulcer | Leg ulcers | Carcinoma sigmoid | Chronic pancreatitis | Carcinoma esophagus | Myelopathy | Retroperitoneal abscess; Ca colon | Osteomyelitis |
| Number of infusions | | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| BSP, % retention | Before infusion | 1 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 5 |
| | After 14 infusions | 8 | 21 | 12 | 8 | 16 | 6 | 11 | 8 | 17 | 10 |
| | 7–21 days after last infusion | 1 | 21 | 2 | 3 | 6 | 5 | 4 | 4 | 11 | 2 |
| Thymol turbidity units | Before infusion | 1.0 | 1.2 | 4.6 | 2.7 | 5.3 | 0.5 | 2.0 | 2.9 | 9.2 | 5.5 |
| | After 14 infusions | 3.2 | 1.5 | 18.5 | 2.4 | 6.4 | 2.0 | 4.5 | 5.0 | 13.0 | 4.1 |
| | 7–21 days after last infusion | 5.0 | 0.5 | 7.9 | 0.6 | 2.5 | 5.0 | 3.2 | 4.2 | 11.6 | 3.2 |
| Cephalin flocculation | Before infusion | 1+ | 3+ | 2+ | 2+ | 3+ | 4+ | 2+ | 1+ | 3+ | 3+ |
| | After 14 infusions | 1+ | 3+ | 1+ | 3+ | 2+ | 3+ | 1+ | 3+ | 3+ | 2+ |
| | 7–21 days after last infusion | — | 3+ | — | 3+ | 3+ | 4+ | 1+ | 1+ | 3+ | 3+ |
| Total bilirubin, mg/100 ml. | Before infusion | 0.4 | 0.8 | 0.4 | 0.9 | 0.7 | 0.5 | 0.6 | 0.9 | 0.2 | 0.5 |
| | After 14 infusions | 0.5 | 0.7 | 0.4 | 0.6 | 0.7 | 0.4 | 0.5 | 0.8 | 0.4 | 0.3 |
| | 7–21 days after last infusion | 0.6 | 1.0 | 0.2 | 0.9 | 0.7 | 0.4 | 0.6 | 0.7 | 0.6 | 0.4 |
| Urine urobilinogen, units | Before infusion | 1.3 | 5.7 | 0.5 | 0.2 | 1.6 | 0.2 | 0.5 | 5.6 | 0.3 | 0.5 |
| | After 14 infusions | 0.6 | 1.6 | 0.4 | 1.6 | 0.4 | 1.0 | 3.5 | 3.5 | 0.6 | 0.5 |
| | 7–21 days after last infusion | 0.9 | 8.3 | 0.4 | 1.1 | 1.5 | 1.1 | 2.9 | 4.1 | 1.0 | 0.6 |
| Serum protein, gm. % | Before infusion | 7.0 | 8.2 | 8.4 | 7.8 | 7.3 | 7.1 | 6.3 | .. | 7.5 | 6.3 |
| | After 14 infusions | 7.3 | 6.5 | 7.8 | 7.5 | 7.5 | 7.1 | 6.6 | 8.3 | 7.7 | 6.7 |
| | 7–21 days after last infusion | 7.5 | .. | .. | 6.9 | .. | 8.5 | 6.5 | 6.7 | .. | .. |
| GOT units | Before infusion | 23 | 37 | 18 | 18 | 18 | 44 | 23 | 61 | 16 | 17 |
| | After 14 infusions | 24 | 12 | 7 | 23 | 31 | 18 | 20 | 52 | 26 | 23 |
| | 7–21 days after last infusion | 31 | 21 | 19 | 24 | 21 | 17 | .. | 42 | 31 | 29 |
| LDH, units | Before infusion | 49 | 12 | 20 | 16 | 79 | 35 | 31 | 28 | 12 | 14 |
| | After 14 infusions | 10 | 25 | 15 | 25 | 39 | 21 | 19 | 12 | 12 | 12 |
| | 7–21 days after last infusion | 12 | 21 | 20 | 16 | 15 | 19 | .. | 16 | 20 | 23 |
| Blood prothrombin content, % | Before infusion | 74 | 87 | 100 | 100 | 70 | 73 | 76 | 55 | 100 | 87 |
| | After 14 infusions | .. | 76 | 87 | 100 | 87 | 29 | 87 | 89 | 100 | 84 |
| | 7–21 days after last infusion | .. | .. | .. | 87 | .. | 63 | 74 | 87 | .. | .. |

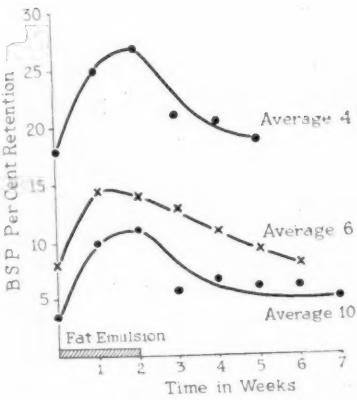


Fig. 1.—Sulfobromophthalein U. S. P. (Bromsulphalein) retention in 20 patients who received intravenous fat emulsion for two weeks. Ten had sulfobromophthalein retention of 5% or less before the infusions. Six had preinfusion retention of 6% to 14%, inclusive; four had preinfusion retention of 15% or more.

turbidity was measured at least 12 hours after the fat infusion had been completed.

Liver biopsies were performed in 11 patients before and after the courses of infusion. The preinfusion biopsy specimens obtained at laparotomy (10 cases) or by needle biopsy (1 case) 1 to 17 days prior to the infusions. The postinfusion biopsies were done one day after the last infusion in four cases, two days afterward in five cases, seven days afterward in one, and eight days afterward in one. They were obtained at laparotomy under local anesthesia (five cases) or by the Zieve modified "Vim"-Silverman needle using a percutaneous transthoracic approach (six cases). The sections were stained with hematoxylin and eosin and by Oil-Red O for fat. Six of the patients with biopsies had normal sulfobromothalein retention, and five had abnormal retention prior to the infusions.

## Results

*Sulfobromophthalein.*—The most marked effect of the fat infusions on liver function was on the retention of sulfobromophthalein. The results of dye retention tests in 10 patients with normal initial dye retention and in 10 patients with abnormal initial dye retention are given in Tables 2 and 3. Figure 1 summarizes the data. There was an increase of sulfobromophthalein retention in all patients during the periods of infusions, although in six patients (Patients 4, 6, 8, 11, 12, and 16) this was only a small amount (an increase of less than 4% retention). In 15 patients there was a return to approximately preinfusion levels in three weeks or less after the last infusion. No postinfusion dye retention test was obtained in one of the five remaining patients. Of the other four, two returned to preinfusion status between three and six weeks after the last infusion, and two had persistent increased impairment of ability to clear sulfobromophthalein. One of these (Patient 18) was proved to have hepatic metastases at autopsy, and the other (Patient 9) is living but is suspected of having hepatic metastases from carcinoma of the colon.

*Thymol Turbidity and Flocculation.*—In 15 of the 20 cases the preinfusion thymol turbidity was normal. Five of these developed abnormal turbidity during the course of the infusions with return to normal within one to three weeks after the last infusion in three. In the fourth patient (Patient 3) the thymol turbidity was elevated seven days after the last infusion but was normal four months later. The fifth case (Patient 18) had a persistently elevated thymol turbidity, probably on the basis of hepatic metastases from carcinoma of the stomach.

In the five patients with abnormal thymol turbidity prior to the infusions, there was an increase in turbidity in all except one (Patient 10) with return to approximately preinfusion levels after the last infusion in three. One (Patient 15) had a persistently elevated turbidity.

Thymol flocculation was negative in all except Patient 17. This patient had portal cirrhosis. The thymol flocculation was 3+ before the infusions, was negative during the infusions, and was 1+ or 3+ on several occasions after the infusions were completed.

*Cephalin Flocculation.*—Of the 12 patients in whom the cephalin flocculation was normal prior to the infusions, 7 developed an abnormal flocculation during the

TABLE 3.—*Liver Function Tests in Patients with Abnormal Sulfobromophthalein (Bromsulphalein) Retention Prior to Infusion*

| Patient | | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, yr. | | 40 | 53 | 76 | 35 | 67 | 63 | 44 | 59 | 65 | 51 |
| Diagnosis | | Incisional hernia | Duodenal ulcer | Carcinoma stomach | Hemiplegia | Carcinoma pancreas | Carcinoma lung | Portal cirrhosis | Carcinoma stomach | Carcinoma rectum | Osteomyelitis |
| Number of infusions | | 14 | 14 | 19 | 14 | 17 | 14 | 14 | 14 | 14 | 14 |
| BSP, % retention | Before infusion | 6 | 6 | 7 | 9 | 11 | 11 | 15 | 16 | 21 | 25 |
| | After 14 infusions | 9 | 9 | 17 | 19 | 26 | 13 | 26 | 25 | 41 | 29 * |
| | 7–21 days after last infusion | 4 | 8 | 10 | 11 | 22 | 5 | 14 | 32 | -- | 16 |
| Thymol turbidity, units | Before infusion | 2.7 | 1.4 | 4.6 | 2.7 | 6.8 | 2.2 | 8.6 | 2.9 | 0.6 | 2.5 |
| | After 14 infusions | 4.0 | 1.8 | 8.4 | 6.4 | 16.5 | 4.6 | 21.3 | 6.2 | 2.7 | 9.2 |
| | 7–21 days after last infusion | 4.0 | 2.0 | 2.9 | 4.0 | 13.0 | 2.5 | 11.3 | 14.5 | 2.0 | 2.9 |
| Cephalin flocculation | Before infusion | 3+ | -- | 3+ | ± | 2+ | 3+ | 1+ | 1+ | 1+ | -- |
| | After 14 infusions | 3+ | 2+ | 3+ | 3+ | 4+ | 3+ | 3+ | 2+ | 3+ | 3+ |
| | 7–21 days after last infusion | 2+ | -- | 4+ | 3+ | 4+ | 2+ | 2+ | 3+ | 2+ | 1+ |
| Total bilirubin, mg/100 ml. | Before infusion | 0.3 | 0.8 | 0.7 | 0.5 | 0.3 | 0.5 | 0.6 | 0.8 | 0.4 | 0.4 |
| | After 14 infusions | 0.4 | 0.7 | 0.4 | 0.6 | 1.8 | 0.4 | 0.7 | 1.0 | 1.6 | 0.4 |
| | 7–21 days after last infusion | 0.4 | 0.4 | 0.6 | 0.5 | 0.6 | 0.3 | 0.6 | -- | -- | 0.6 |
| Urine urobilinogen, units | Before infusion | 1.4 | 1.0 | 1.1 | 0.3 | 0.3 | 0.7 | 0.7 | 0.9 | 0.4 | 1.8 |
| | After 14 infusions | 1.5 | 0.7 | 0.8 | 0.5 | 0.6 | 1.1 | 0.9 | 2.0 | 0.3 | 0.8 |
| | 7–21 days after last infusion | 1.5 | 0.9 | 0.6 | 0.4 | 0.1 | 0.3 | 0.5 | 0.4 | 1.6 | 2.3 |
| Serum protein, gm. % | Before infusion | 7.2 | 7.8 | -- | 8.6 | 5.6 | 7.6 | 7.7 | 6.5 | 5.5 | 8.7 |
| | After 14 infusions | 6.9 | 7.5 | | 6.8 | 5.8 | 6.3 | 9.3 | 5.3 | 6.7 | 7.3 |
| | 7–21 days after last infusion | -- | 8.2 | | 6.3 | 7.2 | -- | 7.9 | -- | -- | 7.1 |
| GOT, units | Before infusion | 33 | 19 | -- | 24 | -- | 18 | 43 | 22 | 19 | 128 |
| | After 14 infusions | 18 | 21 | | 18 | -- | 23 | 37 | 29 | 50 | 35 |
| | 7–21 days after last infusion | 22 | 17 | -- | 17 | -- | 22 | 42 | -- | 29 | 61 |
| LDH, units | Before infusion | 19 | 9 | -- | 25 | -- | 12 | 15 | 15 | 26 | 16 |
| | After 14 infusions | 16 | 24 | -- | 16 | -- | 12 | 25 | 14 | 18 | 16 |
| | 7–21 days after last infusion | 20 | 25 | -- | 23 | -- | 23 | 31 | -- | 35 | 31 |
| Blood prothrombin content, % | Before infusion | 52 | 87 | -- | 87 | -- | 100 | 100 | 74 | 74 | 100 |
| | After 14 infusions | 100 | 51 | -- | 87 | -- | 100 | 76 | 35 | 100 | 87 |
| | 7–21 days after last infusion | -- | 52 | -- | 89 | -- | 46 | 42 | -- | -- | 100 |

* Obtained after eight infusions.

course of infusions, with return to normal in 4.

The eight patients with elevated preinfusion cephalin flocculation showed no significant changes.

*Urine Urobilinogen.*—Urine urobilinogen was normal in 11 patients and became elevated during the infusions in 4. Two of these returned to the preinfusion levels within one to three weeks, and two remained abnormal. In the other patients inconsistent changes occurred in the value of urine urobilinogen.

The changes in urobilinogen in all patients were of a minor degree, and no significance is attached to them.

*Serum Turbidity.*—Increase in fasting serum turbidity, varying from 40% to 84% transmission, which persisted for more than 24 hours, developed in eight patients during the time the infusions were given. Six of these patients were in good nutritional status and would not ordinarily require the caloric supplement of fat emulsions. The greatest turbidity, ranging from 40% to 75% transmission, was seen in Patient 17, who had portal cirrhosis. The turbidity in the other patients ranged from 60% to 84% transmission. In all cases the serum turbidity returned to normal within one week after the last infusion.

*Other Tests.*—No changes in serum bilirubin, total serum protein, albumin-globulin fractions, prothrombin time, serum glutamic oxalacetic transaminase or serum lactic dehydrogenase attributable to the fat emulsion were observed.

*Liver Biopsies.*—Liver biopsies in 11 cases showed no changes in architecture or any abnormal accumulation of fat in the postinfusion biopsy specimens, as compared with the preinfusion biopsy tissues in either the sections stained by hematoxylin and eosin or in the sections stained by Oil-Red O for fat.

## Comment

McKibbin, Ferry, and Stare [11] showed that the administration of intravenous fat emulsions to dogs for four to six weeks produced a reversible impairment of hepatic function as measured by sulfobromophthalein retention, cholesteremia, and increased cholesterol content of the liver.

The effects of repeated infusions of fat emulsions into humans for long periods of time have also been reported. Jordan [5] gave 10 consecutive daily infusions of 600 ml. each (Lipomul-I. V.) to 11 seriously ill patients and found no evidence of alteration of liver function.

Watkin [18] administered 22 to 36 daily 600 ml. infusions of an emulsion (Lipomul-I. V.) to eight patients, with results on liver function similar to those in our patients. There was an increase in sulfobromophthalein retention in all during the period of the infusion, although in some the effect was slight. Clearance of sulfobromophthalein returned to preinfusion status after the infusions were discontinued, except in one patient with malignant disease. Other liver function tests were less regularly affected.

Care must be taken in evaluating the effect of fat emulsions on liver function in patients who have recently had surgical operations. Tagnon, Robbins, and Nichols [16] showed that a marked increase in the amount of sulfobromophthalein retained in the blood occurs immediately after an operation as the result of surgical trauma, or general or spinal anesthesia. For this reason infusions of fat were not given to the 10 patients in our series who had surgical operations until sulfobromophthalein retention had returned to preinfusion status. Figure 2 illustrates such a patient (Patient 7, Table 2).

This 63-year-old man had a right colon esophagoplasty for carcinoma of the esophagus. His sulfobromophthalein retention was 4% prior to surgery and was 23% two days after. On the 16th postoperative day his sulfobromophthalein retention had returned to the preoperative level of 4%. It subsequently rose to 12% while the patient was receiving fat emulsions but returned to 4% after the infusions were

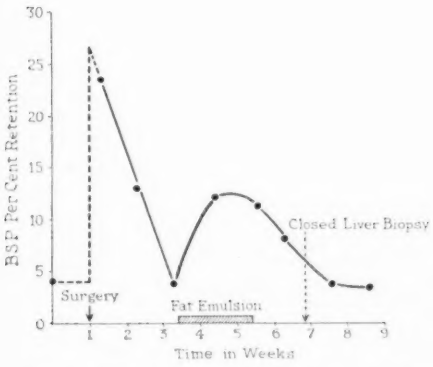


Fig. 2.—Effect of a major operative procedure followed by 14 consecutive daily infusions of a fat emulsion on sulfobromophthalein retention.

discontinued. In the 10 cases in which an operation was performed, the surgical procedure more markedly increased the retention of sulfobromophthalein than did the subsequent infusions of fat.

Waddell and associates [17] reported the effects on liver function of emulsions of 15% coconut or olive oil given to 21 patients. Some of the changes in sulfobromophthalein retention in their patients may have been caused by surgical operations or by the patient's disease. They concluded that the repeated intravenous administration of large quantities of the fat emulsion under investigation had no deleterious effect upon hepatic function. We are in agreement that the liver can tolerate relatively large amounts of infused fat. However, the changes in liver function tests observed in our patients are not the results of surgical procedures or the patient's disease and must be attributable to the fat infusions. The data indicate that hepatic impairment results from continued daily infusions.

Relatively few studies have included postmortem or biopsy material from patients who have received intravenous fat emulsions, in large amounts or for long periods of time. Gorens and associates [3] autopsied a 7-week-old infant who died after receiving 30 to 150 ml. of intravenous fat daily for 11 days, and found that the fat produced no pathologic changes. Lehr and associates [9] found that the organs of three patients who received 19, 20, and 25 daily infusions of 600 ml. of Lipomul-I. V., respectively, showed no abnormal deposits of fat. Shafiroff and Mulholland's [15] patients received 1 liter of 15% or 20% fat daily for 4 to 11 days. There was no histological evidence of kidney, lung, or liver damage in autopsy or biopsy specimens.

Mueller,[12] Lehr and associates,[9] and Glas and Birkelo [2] have called attention to the deposition of a golden-brown pigment in the Kupffer cells and in the parenchymatous cells adjacent to the central vein in patients who received intravenous fat. The exact nature of the pigment is unknown, and it did not react to fat stains. It appeared to be a reversible reaction, and biopsy specimens obtained eight days following fat therapy failed to demonstrate it. Eight patients who received 2 or more 600 ml. units showed an increase in this pigment.[2] Kern and associates [7] also noted this pigment but stated it was small and inconspicuous and often overlooked.

When this finding was called to our attention, we reviewed all liver biopsy tissue, paying particular attention to those of nine patients made within 48 hours after the last fat infusion. Although pigment fitting the description noted above was seen in a few sections, there seemed to be no difference in the appearance between pre- and postinfusion biopsies.

The presence of fat as revealed by histologic study of organs probably depends upon the amount of intravenous fat given and how soon afterward the tissues are examined. Watkin [28] demonstrated accumulations of sudanophilic material in the sinusoidal macrophages of the liver in a patient who had 25 consecutive daily infusions.

These reports substantiate our own experience with 600 ml. infusions of fat, which may be given by daily injection for

14 days without detectable histologic changes in the liver.

## Summary

Liver function studies were done on 20 patients who received 600 ml. of an intravenous fat emulsion daily for 14 to 19 consecutive days. Ten patients had normal and ten had abnormal sulfobromophthalein retention before the infusions.

There was temporary impairment of hepatic function, as indicated by increase in sulfobromophthalein retention in all patients and increase in thymol turbidity and cephalin flocculation in some.

There was return to preinfusion levels of these liver function tests in one to six weeks after the last infusion.

Liver biopsies after the courses of infusion showed no accumulation of fat, as compared with preinfusion biopsies.

Fasting serum turbidity became abnormal in eight patients receiving the infusions but returned to normal within seven days after the infusions were terminated.

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## DISCUSSION

DR. GEORGE C. HENEGAR, Chicago: I would like to point out several features that I think are rather important from a clinical standpoint.

The need for nutritional supplement in the chronically ill and malnourished patient has long been apparent. The use of amino acid or protein supplements in the face of an inadequate caloric intake has not met the need for protein synthesis in the postoperative patient.

The available preparations, such as the various carbohydrate solutions, alcohol, and amino acids, cannot be given parenterally in adequate quantities to meet the metabolic needs without fear of overhydration. The fat emulsions would seem to meet this need if they can be safely used.

A 10% to 15% fat emulsion would provide adequate calories in a relatively small fluid volume. Many such preparations have been tried, both experimentally and clinically, with considerable disappointment. The results of the present study indicate that the preparation we used causes few or no side-effects when properly administered.

The changes in liver function described by Dr. Preston are less striking than those produced by a surgical procedure under general anesthesia. These changes are reversible during the period of postoperative convalescence.

Studies of the effect of these caloric supplements on the reversal of postoperative negative nitrogen balance have shown some indication that the degree of this negative balance is reduced during the postoperative period.

More promising are the studies on nonsurgical patients being maintained on parenteral solutions consisting of carbohydrates, amino acids, and fat infusions. These patients can be maintained in positive nitrogen balance on this program. This means that in those states in which there is interference with nutrition as a result of the disease process, that is, obstructed esophageal lesions, pyloric obstruction, and so forth, the patient can be better prepared nutritionally for surgery, thus giving him more protein for tissue synthesis postoperatively.

DR. WARREN H. COLE, Chicago: We have been using this same emulsion, and we are also very favorably impressed with it, from numerous standpoints. Our data are very similar to those just presented.

I might say that two residents, Dr. Mark Smith and Dr. William Marshall, have been collecting these data. Their data are quite similar to those which has been presented by Dr. Preston and his associates, except that we have not given the detailed attention to the liver function test, which I am glad to hear reported by them.

We might ask ourselves this question: Is this retension of sulfobromophthalein (Bromsulphalein) serious? You will recall that Dr. Preston stated that the retention of the sulfobromophthalein was much more prominent than the abnormality in the other tests. I personally do not believe it is significant at all. We know that several things, including a little interference with the blood supply to the liver, will create a slight retention of the sulfobromophthalein.

The sulfobromophthalein test reveals retention after operation, as Dr. Henegar illustrated. This retention is no greater than that produced by an operation. I doubt very much, therefore, whether this retention has any clinical significance; however, it is a good thing to study and to keep in mind in case liver impairment exists in patients to whom one contemplates giving fat.

In a few of our patients we found a moderate blood pressure elevation, which we thought was insignificant because we often see such changes after transfusions and administration of other intravenous fluids. We noted fever occasionally, but often the injection can be repeated the next day without a febrile reaction.

We were not at all alarmed with the febrile reactions encountered. Our impression is that this material is really entirely safe if one uses the same precautions and judgment one would with any other intravenous solution. The emulsion is not yet on the market. I think it will be soon, for I believe it to be a very useful agent.

DR. EDWIN H. ELLISON, Columbus, Ohio: I would like to congratulate Dr. Preston on his thorough observations, and I agree with Dr. Cole that intravenous fat emulsions should be available for general use in the very near future.

We have given 277 infusions to 42 patients, each receiving from ½ to 28 units. We have had only six reactions, characterized by fever, chills, and tachycardia, severe enough to require discontinuance of the infusion. Four of these occurred with the first infusion; however, we found we could later give a second infusion to these same patients with no difficulty. Several others had minor temperature elevations.

Dr. Mueller, one of our associates, has recently given intravenous fat to patients and animals with obstructive jaundice and found that the infusions were tolerated very well.

(Slide) The comparison of turbidity of serial samples of serum, i. e., prior to infusion and 1, 6, and 12 hours after infusion, shows that clearing occurs equally rapidly in jaundiced patients. Hemolysis did occur in rare instances, as shown by the reddish serum in this specimen.

(Slide) Several patients with severe pancreatic disease or total pancreatectomy have presented a picture similar to that described as an essential fatty acid deficiency in animals. Alopecia, lack of appetite, failure to gain weight in spite of an adequate caloric intake, and swelling of the joints were present. In these patients, infusion of Lipomul-I. V. for a short period of time resulted in an improvement in the patient's nutritional status which was far out of proportion to the calories given and raised the question of whether or not an essential fatty acid has been supplied. This slide demonstrates the response to intravenous fat emulsion in one patient following subtotal gastrectomy and total pancreatectomy for an ul-

cerogenic tumor of the pancreas. It is my contention that essential fatty acid deficiencies play some role in the nutritional problems of the patients with pancreatic disease.

DR. LAWRENCE STRENGER, Columbus, Ohio: How long will this emulsion hold up, and how long is it feasible for a hospital to hold it?

DR. FREDERICK W. PRESTON, Chicago: To answer Dr. Strenger's question, no one knows exactly how long this fat emulsion will remain safe to give to patients. Patients have received fat emulsions that were approximately 6 months old, without any ill effect.

There is one comment I should like to make briefly, shown on the last slide.

(Slide) Fat emulsions affect blood coagulation. This slide shows the effect of the emulsion as determined by two clotting tests. The lower graph shows the lipemic effect produced by the emulsion, and above, the effect on the whole-blood-clotting time. This curve is the prothrombin time.

These tests indicate there is a hypercoagulability of blood. In other words, the coagulability of blood is increased by the fat emulsion during the phase of the lipemia. The effect is not very marked, but it is quite definite. Here are some control studies in which dextrose solution was used, and it had no effect on blood coagulation.

# Significance of the Fall of Serum Sodium Following Operative Trauma

CARL H. ALMOND, M.D., and ROBERT E. L. BERRY, M.D., Ann Arbor, Mich.

The etiology of the often-observed fall of the serum sodium following operation or severe trauma has been principally related to two possible factors: (1) dilution of the extracellular fluid secondary to the use of parenteral fluids, and (2) disturbances in the integrity of the cell membrane which permit augmented increments of intracellular water and electrolyte to pass into the extracellular fluid and a transfer of extracellular sodium into the cells of the various body tissues.[2,4,9,10] Regardless of the relative contributions of these two factors to the observed phenomenon of sodium fall, it is recognized that the serum sodium is restored to previously observed normal levels, without sodium salt administration, provided that internal homeostasis is supported by an early adequate return of oral intake and that extrarenal loss of body fluids is not of a clinical significance.

Modifications of internal exchange between the constituents of the intracellular and of the extracellular fluid compartments have not lent themselves well to accurate measurement and assay of cause. Although the fall in serum sodium following operation is often relatively insignificant and readily self-correctable, its cause remains of considerable interest. This report deals with the attempts to examine certain facets of this problem by comparing the exchangeability of $Na^{22}$, serum sodium concentration, and serum osmolality in patients receiving "conventional" parenteral fluids with similar values for patients who essentially received no water, dextrose, or sodium salts during the first 72 postoperative hours.[12]

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## Methods

Six patients have been studied, four being submitted to "routine" fluid replacement and two being "dehydrated." Except for one patient with mitral valvuloplasty, the subjects were considered to be free of significant cardiovascular and renal disease. Both dehydration studies were done in patients who were considered quite capable of withstanding the withholding of fluids for a period of 72 hours.

Three microcuries of $Na^{22}$ was injected 24-36 hours prior to operation, a period of time which permits maximum practical exchangeability of this isotope to occur. $Na^{22}$ has a half-life of 2.6 years and a biological half-life of 19-29 days. Because of a relatively long half-life, repeated samplings of the specific radioactivity of serum were permitted without consideration of a decay factor. This technique does not submit any patient to undue radiation hazard. Venous blood samplings and urine outputs were obtained at specific intervals varying from 5 to 24 hours during the postoperative period. Blood was centrifuged within 30 minutes and the serum drawn off. Three separate 1 ml. samples were timed and counted for 6400 counts in scintillation well counters. The standard, consisting of 1 ml. of the injected solution diluted 250 times, was similarly determined by three separate 1 ml. specimens timed for a period of 6400 counts. The radioactivity of excreted urine and extrarenal fluid loss was similarly determined. Exchangeability of $Na^{22}$, measured as milliequivalents per kilogram of body weight, was determined by the following formula:

$$Na_e = \frac{Na_I - Na_u}{Na_s/NamEq/kg}$$

Where $Na_e$=exchangeable sodium, in milliequivalents per kilogram; $Na_I$=counts per milliliter per second of injected $Na^{22}$; $Na_u$=counts per milliliter per second of urine and extrarenal loss×volume, in milliliters; $Na_s$=counts per milliliter per second

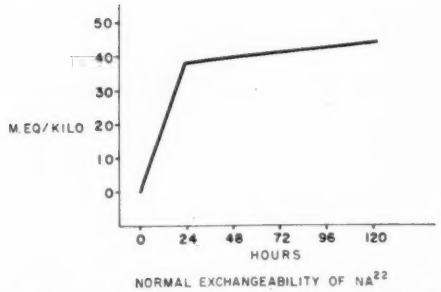



Fig. 1.—Exchangeability of $Na^{22}$ observed in normals. Exchangeability is, for practical purposes, complete in 24 hours. A slight increase has been observed as long as four weeks (after Streeten[11]).

of serum; $Na_{mEq.}$ = serum concentration sodium, in milliequivalents per milliliter, and kg. = body weight in kilograms.

Serum and urine sodium were simultaneously determined by using the Beckman flame photometer, Model DU, duplicate determinations being done whenever possible. Osmolality was determined with the Fiske osmometer.

The only fluids administered during dehydration studies were those administered by slow drip in order to keep an intravenous needle open for the purpose of facilitating whole-blood infusion during operation.

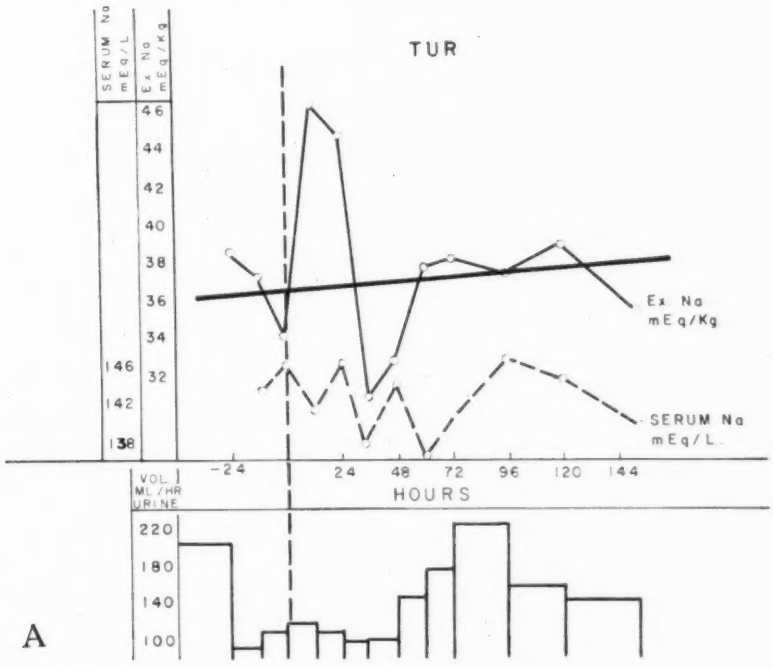
## Results

*Equilibration of $Na^{22}$ in Normal Subjects.*—Controls in normals have demonstrated rapid dilution of the isotope during the first 24 hours, followed by a consistent leveling out of exchangeability at that time (Fig. 1). Subsequently there is a gradual increase in the net measurable specific serum radioactivity that suggests incorporation of isotope into the metabolic activity of cells and/or bone.[4,10] The average exchangeability was approximately 42 mEq/kg., a figure comparing favorably with that observed for $Na^{24}$.[3,6,8] Streeten[11] has observed a slight gradual increase in serum-specific radioactivity in controls observed for four weeks.

*"Conventional" Administration of Parenteral Fluids.*—Four patients receiving whole-blood replacement during operation, followed by the administration of 1000-1500 ml. of 5% dextrose and water with or without 0.2% NaCl during the day of operation and then returning to oral intake within 48 hours, tend to produce a pattern characterized by a marked increase in exchangeable sodium during the first 12-24 hours. Detailed data are presented for only two of these cases (Figs. 2 and 3; Tables 1 and 2). This increase may, however, be followed by a "rebound phenomenon," in which the exchangeability falls as much as 16% below previously observed "normal" levels (Fig. 2). The marked increase followed by the "rebound" of the exchangeable sodium has usually run its course after 24-48 hours. This is then followed by a return to "normal" specific serum radioactivity compatible with the anticipated gradual increase in sodium exchangeability estimated from that observed in normals.

Patient A (Table 1 and Fig. 2) demonstrated a 27% increase in exchangeable sodium at the 11th postoperative hour. By the 35th postoperative hour this value had fallen more than 16% below the "normal" value observed before operation. This was accompanied by a 4%-5% fall in the concentration of the serum sodium.

Patient B was studied after mitral valvulotomy. Many observations on the fall of serum sodium concentration and osmolality have previously been made after operation upon patients of this type. These studies have suggested that the response in this group is "exaggerated" and the fall of greater magnitude, although the mechanism has not been entirely pinpointed.[1,7,13] The maximum increase in exchangeable sodium of 17% was observed at the 17th postoperative hour, falling by the 26th hour to a value of 2.5% less than the preoperative "normal" level. Although exchangeable sodium levels rapidly stabilized, the fall in serum sodium was sustained longer, a maximum decrease of 5.7% being observed at the 94th postoperative hour (Fig. 3 and Table 2). Urine sodium concentrations were abnormally low throughout the study and showed little change following the onset of diuresis at the 70th hour, which was



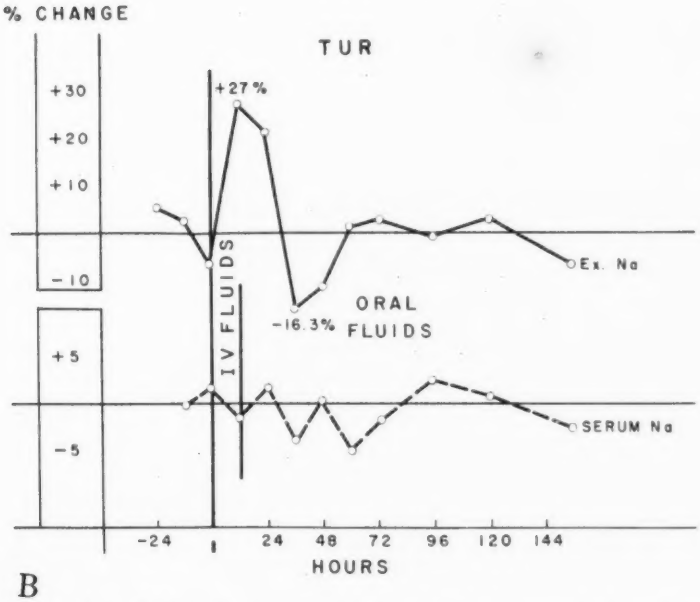
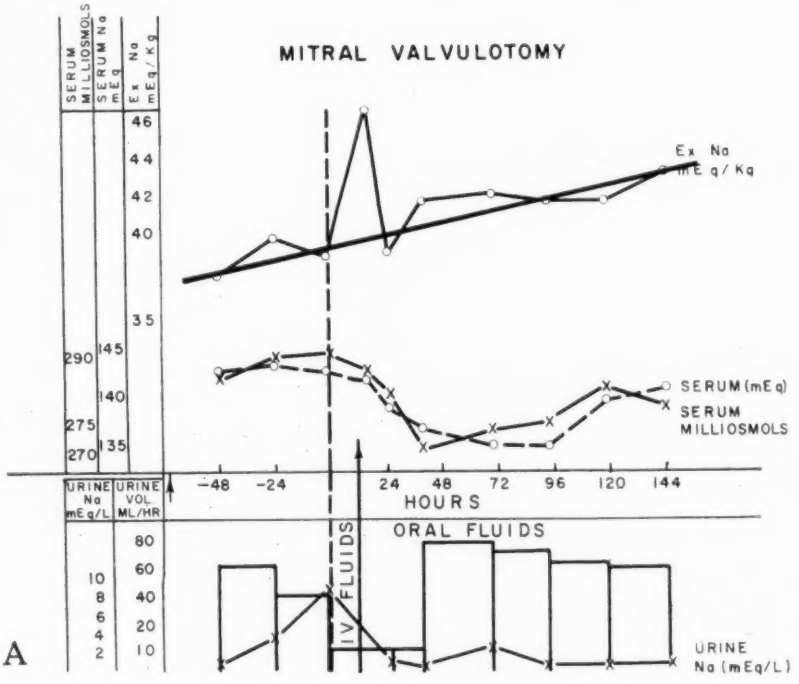




Fig. 2.—(*A*) Patient A, a man aged 65, undergoing transurethral resection. Graphic demonstration of exchangeable sodium, serum sodium concentration, and urine output during 144 postoperative hours. The patient received 500 ml. of whole blood and 1000 ml. of 5% dextrose and water in 0.2% NaCl during and immediately after operation. He was then started on oral fluids.

(*B*) A 27% increase in exchangeable sodium has been followed by 16% fall during the first 36 hours. Serum sodium changes demonstrate lowered levels after a return to exchangeable sodium to observed preoperative "normal" levels.



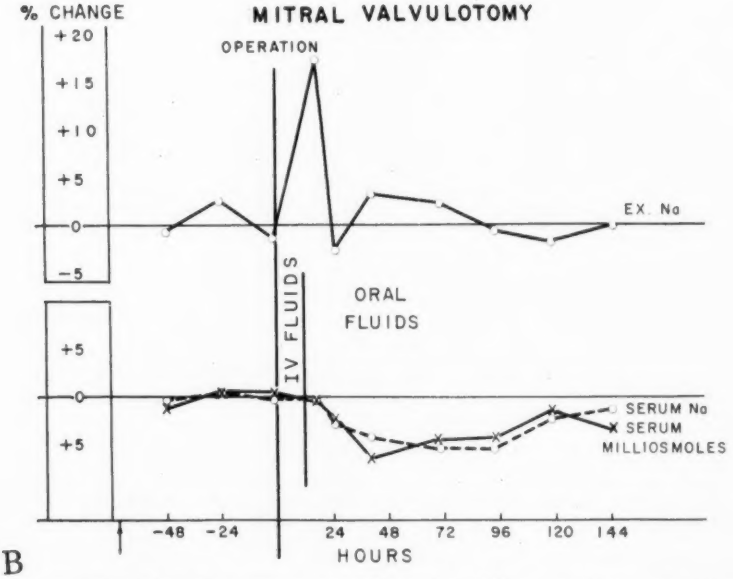




Fig. 3.—(*A*) Patient B, a woman aged 52, received 1000 ml. of blood and 1300 ml. of 5% dextrose and water in 0.2% NaCl during and immediately after surgery. A sharp increase in exchangeable sodium returned to "normal" after 24 hours. Serum sodium and osmolality fell sharply and tended to parallel each other.

(*B*) Percentage changes in exchangeable sodium, serum sodium, and osmolality. Serum sodium and osmolality did not return to normal until about the 144th postoperative hour. Urinary excretion of sodium was extremely small even after the onset of diuresis, at about the 48th hour.

TABLE 1.—*Data on a Sixty-Seven-Year-Old Man (Patient A) Undergoing Transurethral Resection of Prostate**

| Time, Hr. | Exchangeable Na mEq/Kg. | Variation, % | Serum Na, mEq/L. | Variation, % | Urine | |
|---|---|---|---|---|---|---|
| | | | | | Vol., Ml. | Ml/Hr. |
| −24.8 | 38.5 | 5.4 | | | 2210 | 200.9 |
| −12.8 | 37.1 | 2.5 | 143.3 | −0.1 | 1100 | 91.7 |
| −1.2 | 34.0 | −6.3 | 146.0 | 1.7 | 1280 | 109.8 |
| 11.0 | 46.9 | 27.0 | 141.3 | −1.5 | 1455 | 119.6 |
| 23.0 | 44.6 | 21.7 | 146.2 | 1.9 | 1310 | 109.2 |
| 35.6 | 30.8 | −16.3 | 137.8 | −4.0 | 1235 | 98.2 |
| 47.0 | 32.8 | −11.4 | 144.0 | 0.3 | 1155 | 101.1 |
| 60.0 | 37.6 | 1.6 | 136.3 | −5.0 | 1880 | 144.6 |
| 73.6 | 38.1 | 2.6 | 140.8 | −1.9 | 2350 | 173.1 |
| 95.0 | 37.4 | −0.3 | 146.9 | 2.4 | 4770 | 222.7 |
| 119.0 | 39.1 | 2.9 | 144.6 | 0.8 | 3800 | 158.3 |
| 154.6 | 35.4 | −6.9 | 139.5 | −2.8 | 5020 | 141.1 |

* He received 500 ml. of blood and 1000 ml. of 5% dextrose and water on 0.2% NaCl intravenously during and immediately after operation and was then started on oral fluids.

accompanied by an increase in the serum sodium.

*Dehydration Studies.*—Two patients were studied who received no fluids during the first 72 postoperative hours except replacement of whole-blood loss during operation, in addition to adequate parenteral water to keep the intravenous needle open during the operative procedure.

Patient C (Fig. 4 and Table 3) demonstrated a maximum increase of 5.4% of exchangeable sodium during the first 24 hours. This was accompanied by almost insignificant changes in serum sodium concentration and osmolality. Excretion rate of urine fell as low as 14.3 ml. per hour, and excellent conservation of sodium was observed during the period of dehydration.

A similar pattern in exchangeable sodium, serum sodium concentration, and osmolality was observed in the second patient (Patient D; Fig. 5 and Table 4). A maximum increase of 5% in exchangeable sodium was observed at the 52d postoperative hour, accompanied by a slight increase in serum sodium concentration. A sharp drop in osmolality at the 19th hour was accompanied by a decrease in serum sodium of but one-third the amplitude. Urine output fell as low as 15.3 ml. per hour during the period of dehydration. Serum sodium conservation was not as efficient as that observed in Patient C (Table 3).

## Comment

The parameters of the internal exchange of constituents of the extracellular and intracellular fluid compartments in response to the variables of operative stress possess a high degree of complexity. Only a narrow facet of this problem has been surveyed in these studies. The small number of cases studied to date does not permit valid statistical analysis.

The fall in serum sodium and osmolality in response to operative trauma has been a known phenomenon for years. Previous reports have suggested that this is a "dilutional" response to the retention of administered parenteral fluid, an increase of extracellular volume at the expense of intracellular fluid and from the water of oxidation resulting from protein and fat breakdown in the immediate postoperative period.[2,5,9] The withholding of usually administered fluids for 72 postoperative hours has been accompanied by such minimal changes in serum sodium fall and osmolality that they fall almost within the range of laboratory error. These findings would support previous observations of the importance of the dilutional factors.

In previous well-nourished and hydrated patients, free of cardiac, hepatic, and renal disease, the observed fall in serum sodium and osmolality following operative trauma

TABLE 2.—*Data on a Fifty-Two-Year-Old Woman (Patient B) Undergoing Mitral Valvulotomy for Mitral Stenosis* *

| Time, Hr. | Exchangeable Na, mEq/Kg. | Variation, % | Serum Na mEq/L. | Variation, % | Millios-mols | Variation, % | Urine Vol., Ml. | Ml/Hr. | Na, mEq/L. | Na, mEq. |
|---|---|---|---|---|---|---|---|---|---|---|
| −48.8 | 37.6 | −0.5 | 142.8 | −0.1 | 285.5 | −1.1 | 400 | 19.05 | 2.5 | 1.0 |
| −24.3 | 39.9 | 2.8 | 143.2 | 0.2 | 290.0 | 0.4 | 1473 | 60.1 | 2.5 | 3.7 |
| −1.0 | 38.9 | −1.3 | 142.8 | −0.1 | 290.8 | 0.7 | 955 | 41.1 | 9.6 | 9.0 |
| 16.8 | 46.0 | 17.1 | 141.7 | −0.1 | 287.8 | −0.4 | 0 | 0 | 0 | 0 |
| 25.8 | 39.0 | −2.5 | 138.6 | −3.0 | 282.3 | −2.3 | 280 | 11.3 | 4.4 | 1.2 |
| 41.8 | 41.7 | 3.2 | 136.6 | −4.4 | 270.3 | −6.4 | 183 | 11.4 | 2.9 | 0.5 |
| 69.8 | 42.2 | 2.4 | 134.9 | −5.6 | 275.3 | −4.7 | 2294 | 79.1 | 1.1 | 2.5 |
| 94.0 | 41.7 | −0.5 | 134.8 | −5.7 | 276.3 | −4.3 | 1725 | 71.1 | 0.4 | 0.6 |
| 118.8 | 41.7 | −1.9 | 139.5 | −2.4 | 284.0 | −1.7 | 1588 | 64.2 | 0.4 | 0.7 |
| 144.3 | 43.2 | 0 | 141.0 | −1.4 | 279.5 | −3.2 | 1555 | 61.0 | 0.6 | 0.0 |

* She received 1000 ml. of blood and 1300 ml. of 5% dextrose and water in 0.2% NaCl during and immediately after surgery and was then started on oral fluids (Fig. 3).

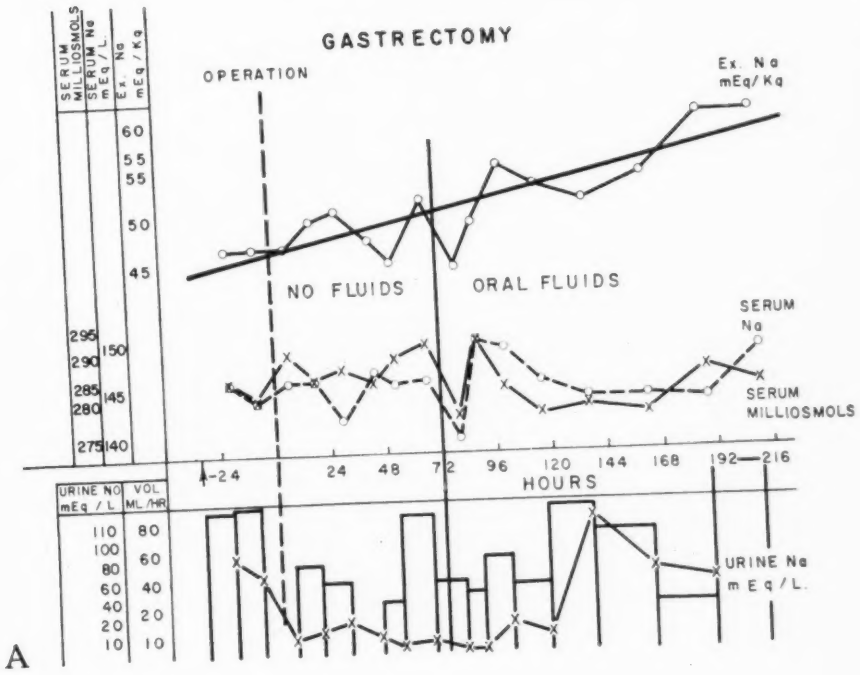
is, for the most part, of little importance. It is self-limiting and self-correctable and does not require vigorous sodium salt therapy. Indeed, it may well be hazardous to initiate vigorous "corrective" therapy for those patients who may demonstrate postoperative acute falls in serum sodium concentration and who have lost considerable weight, or who have been chronically ill or suffer serious cardiac, hepatic, or renal disease prior to operation. Acute postoperative hyponatremia, without symptoms of water intoxication, is best handled by a conservative and gentle approach.

The most striking variable in these studies, however, has not been the differences in the serum sodium concentration and osmolality between the conventional administration or withholding of fluids but the marked percentage differences in exchangeable sodium. The two dehydrated patients demonstrated increases in exchangeable sodium that were but fractions of the changes noted in those conventionally hydrated. Even administration of 1500 ml. of whole blood during operation (Patient C, Table 3 and Fig. 4) did not produce a marked increase in exchangeable sodium.

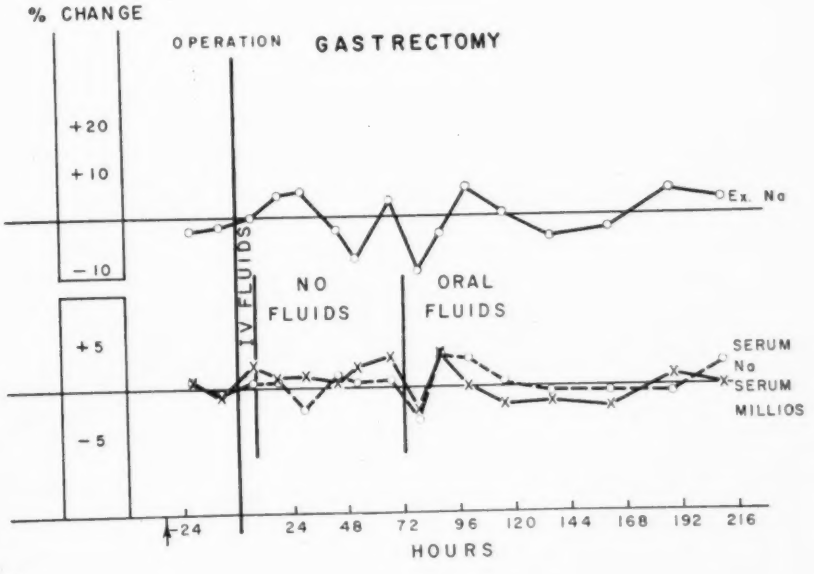
TABLE 3.—*Data on Twenty-One-Year-Old Man (Patient C) with Subtotal Gastrectomy for Duodenal Ulcer* *

| Time Hr. | Exchangeable Na mEq/Kg. | Variation, % | Serum Na mEq/L. | Variation, % | Millios-mols Liter | Variation, % | Urine Vol./Ml. | Ml. Hr. | Na, mEq/L. | Na, mEq. |
|---|---|---|---|---|---|---|---|---|---|---|
| −19.7 | 46.7 | −2.9 | 145.5 | 0.6 | 284 | 0.7 | 1070 | 89.2 | 81.8 | 87.5 |
| −7.7 | 46.9 | −2.0 | 143.7 | −0.6 | 280 | −0.7 | 1100 | 91.7 | 62.5 | 68.6 |
| +5.3 | 46.9 | 0 | 145.6 | 0.7 | 289 | 2.5 | 190 | 14.6 | 7.9 | 1.5 |
| 17.7 | 49.5 | +4.4 | 145.6 | 0.7 | 285 | 1.1 | 620 | 50.3 | 11.9 | 7.4 |
| 28.5 | 50.4 | +5.4 | 141.6 | −2.1 | 286 | 1.4 | 410 | 37.9 | 16.7 | 6.9 |
| 43.5 | 47.5 | −2.7 | 146.8 | 1.5 | 283 | 0.4 | 215 | 14.3 | 8.3 | 1.8 |
| 52.5 | 45.0 | −8.4 | 145.4 | 0.6 | 288 | 2.1 | 220 | 24.4 | 4.3 | 1.0 |
| 66.5 | 51.8 | +3.6 | 145.7 | 0.8 | 291 | 3.2 | 1165 | 83.2 | 5.8 | 6.8 |
| 79.5 | 44.5 | −11.8 | 139.4 | −3.6 | 276 | −2.1 | 483 | 37.2 | 1.9 | 0.9 |
| 88.5 | 49.1 | −3.9 | 149.7 | 3.5 | 292 | 3.6 | 260 | 28.9 | 0.4 | 0.1 |
| 102.5 | 55.2 | +6.9 | 149.0 | 3.0 | 282 | 0 | 755 | 53.9 | 15.9 | 12.0 |
| 115.5 | 53.0 | +0.2 | 145.5 | 0.6 | 276.5 | −2.0 | 440 | 33.8 | 9.1 | 4.0 |
| 137.3 | 51.4 | −4.4 | 143.9 | −0.5 | 277.5 | −1.6 | 1905 | 87.3 | 112.4 | 214.1 |
| 161.8 | 54.0 | −2.7 | 143.9 | −0.5 | 276 | −2.1 | 1715 | 70.0 | 64.6 | 110.8 |
| 187.3 | 60.3 | +5.6 | 143.4 | −0.8 | 285 | 1.1 | 500 | 19.6 | 56.8 | 28.4 |
| 210.8 | 60.2 | +3.4 | 148.4 | 2.6 | 282 | 0 | 2710 | 115.3 | 403.8 | 1094.3 |

* He received no fluids during the first 72 postoperative hours except 1500 ml. of whole blood and 250 ml. of 5% dextrose and water in 0.2% NaCl during operation. At the end of 72 hours he was given 2000 ml. of 5% dextrose and water, followed by 500 ml. of 0.9% NaCl (Fig. 4).



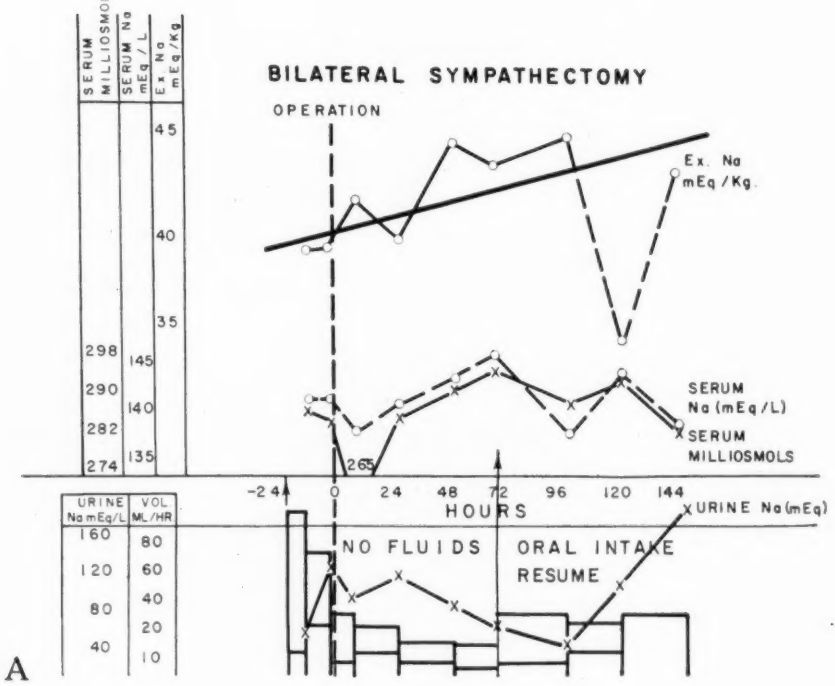

A




B

Fig. 4.—(*A*) Patient C, a man aged 21. Exchangeable sodium, serum sodium, and osmolality following subtotal gastrectomy, with essentially no parenteral water given during the first 72 hours postoperatively. Minimal changes are observed. For the most part urine outputs average between 15 and 40 ml. per hour during the time of dehydration.

(*B*) Graphic presentation of percentage changes observed during 216 postoperative hours. Deviations appear to fall, for the most part, within laboratory error.



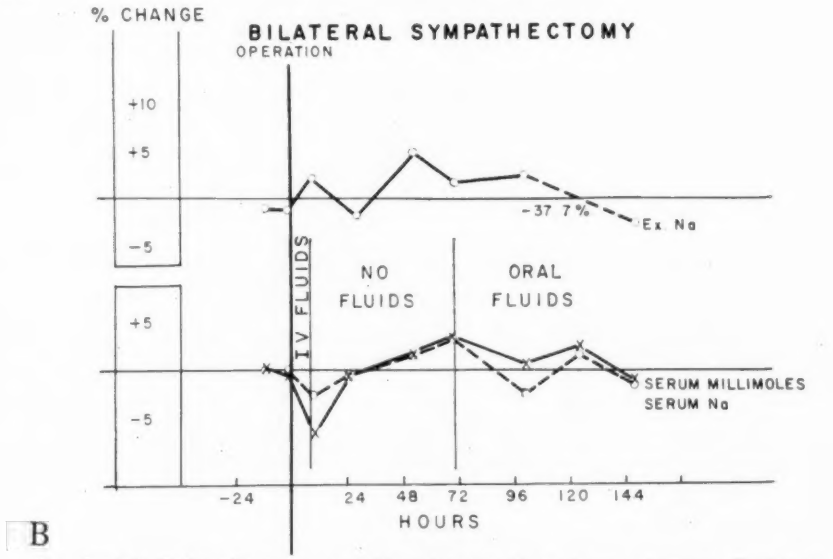




Fig. 5.—(*A*) Patient D, a man aged 53, undergoing bilateral sympathectomy. Exchangeable sodium, serum sodium, and osmolality following bilateral lumbar sympathectomy, essentially no parenteral water being administered during the first 72 postoperative hours. Except for a sharp fall in osmolality during the first 24 hours, changes are minimal. The sharp fall in exchangeable sodium, demonstrated at about the 120th hour, is probably a laboratory error and has been disregarded. Urine output during the dehydration period was between 15 and 30 ml. an hour.

(*B*) Graphic demonstration of percentage changes in exchangeable sodium, serum sodium and osmolality. As in Figure 4, they are, for the most part, almost within the range of laboratory error. The figure of −37.7%, observed at the 120th hour, has been considered a laboratory error and has not been considered.

TABLE 4.—*Data on Fifty-Three-Year-Old Man (Patient D) Undergoing Bilateral Lumbar Sympathectomy* *

| Time, Hr. | Exchangeable Na, mEq/Kg. | Variation, % | Serum Na, mEq/L. | Variation, % | Millios-mols | Variation, % | Urine | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Vol., Ml. | Ml/Hr. | Na, mEq/L. | Total Na, mEq. |
| −11.7 | 39.34 | −1.0 | 141.0 | 0 | 285.5 | +0.4 | 920 | 112.6 | 56.8 | 52.3 |
| −2.2 | 39.54 | −1.2 | 141.0 | 0 | 283.5 | −0.4 | 850 | 75.0 | 128.0 | 108.8 |
| +8.5 | 41.91 | +2.2 | 137.7 | −2.3 | 265.0 | −6.9 | 320 | 30.0 | 92.0 | 29.4 |
| +28.3 | 39.89 | −1.9 | 140.6 | −0.3 | 284.0 | −0.2 | 420 | 21.2 | 114.5 | 48.1 |
| 52.3 | 44.98 | +5.0 | 143.2 | +1.6 | 290.00 | +1.9 | 400 | 16.3 | 83.5 | 33.4 |
| 69.8 | 43.85 | +1.9 | 145.5 | +3.2 | 294.0 | +3.3 | 260 | 15.3 | 61.4 | 16.0 |
| 101.7 | 45.26 | +2.5 | 137.3 | −2.6 | 287.0 | +0.8 | 680 | 24.8 | 42.4 | 28.8 |
| 124.8 | 34.58 | −37.7 | 143.6 | +1.8 | 291.8 | +2.6 | 500 | 21.3 | 106.5 | 53.3 |
| 148.8 | 43.26 | −2.5 | 138.5 | −1.8 | 281.3 | −1.1 | 755 | 31.5 | 189.0 | 142.69 |

* He received no fluids during the first 72 postoperative hours except 400 ml. of 5% dextrose and water during the operation. He resumed oral intake at the end of 72 hours (Fig. 5).

The percentage increase in exchangeable sodium is three to five times the observed fall in serum sodium in the conventional hydrated patients and negligible in the dehydrated patients. A direct relationship may well exist between the increase in exchangeable sodium and the quantitative volume of fluid given parenterally, small increases being observed when no fluids are given and considerable larger values being observed when a greater amount is administered. The mechanisms of the variables in the apparent internal shifts of water and electrolyte have not been provided from the data in these studies but have been a stimulus for further investigation.

## Summary and Conclusions

The exchangeability of $Na^{22}$, serum sodium concentrations, and serum osmolalities have been studied in six patients during the immediate postoperative period. Detailed data are presented in two studies during which "conventional" fluids were used and two in which all fluids were essentially withheld during the first 72 hours.

During the first 24 hours the percentage exchangeability of $Na^{22}$ is considerably greater than the fall in serum sodium and osmolality when conventional fluids are used.

The withholding of fluids during the first 72 hours results in minimal changes in the observed sodium and osmolal concentrations and levels of exchangeable sodium.

It is probable that the fall in serum sodium during the postoperative period is principally a dilutional effect initiated by parenteral infusion and augmented by internal shifts of water and electrolyte.

A lack of correlation between exchangeable sodium and the fall in serum sodium has been observed but cannot be explained from data obtained in these studies.

The fall in serum sodium concentration and osmolality produced by operative trauma is, for the most part, self-limiting and self-correctable and does not require vigorous sodium salt replacement therapy.

Miss Madeline McMath, Miss Emily Dorstewitz, and Miss Sally Stevenson gave technical assistance.

Department of Surgery, University Hospital.

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## DISCUSSION

DR. EDWARD E. MASON, Iowa City: This is the sort of information that we badly need in order to find out what exactly is happening to our patients after surgery with regard to the concentration of sodium and what it means.

All of us need to examine the data from our own laboratories and be aware of the causes of abnormalities in serum sodium concentration, and for that reason I would like to show you an analysis we made at the University of Iowa.

(Slide) This is from recently published work. We took 63 patients whose serum sodium concentration had been very abnormal. This is the normal concentration of sodium, around 140 mEq. per liter. Some of the patients had as low as 110 mEq., and some as high as 180 mEq. We expected that the concentration of chloride and $CO_2$ would vary in the same direction and to the same degree as did the sodium. You will notice that as the sodium concentration goes down, the concentration of these anions goes down, and that as the concentration of sodium increases, the concentration of the anions increases.

As you may have noticed from the paper that was just presented, the changes in concentration of sodium which occur under usual circumstances are not great. We found in our study that these very abnormal concentrations of sodium were not due to surgery; they were not due to trauma, nor were they due to the release of mineralocorticoids, or to an "alarm reaction," although these things may contribute to the abnormality. It could be shown in all these cases that there was good explanation of the abnormality simply on the basis of good old-fashioned intake and output.

(Slide) Here is a little gimmick which may help in explaining this point to your students. It is simply a diagram which has a panel back of the slot for total body water, and a Gamblegram with a panel that slides. These are connected by a lever arm. These two things are reciprocally related; that is, if the total body water is increased by 10%, the concentration of anions in the serum should also go down by 10%. If they do not go down by 10%, the laboratory has made an error. You cannot apply laboratory data to the treatment of patients without first determining that the laboratory data have internal consistency.

(Slide) Likewise, if the volume of total body water is decreased by 10%, there will be an increase in concentration of sodium by 10%, and likewise a 10% increase in the anions.

The reason (which has been stated many times) why chloride plus $CO_2$ is not a good indication of tonicity, and why sodium is a good indication of tonicity, is shown by the fact that the unmeasured anions can change as a result of uremia, diabetic acidosis, or other things. I think if you check on the data in your own hospital laboratory and make a plot of the ratio between Na and $CO_2$ plus Cl, you will get a good idea of whether your laboratory is doing an optimum job.

DR. ROBERT E. L. BERRY, Ann Arbor, Mich.: Technical papers of this type, dealing with the complexities of the internal movement of water and electrolytes, have often been criticized because of impracticability. However, somewhere far down between the milliosmols and the milliequivalents, if sought for assidiously, something that is practical often can be found.

Although our studies were the basis for a broader insight into the complexities of internal exchange, one corollary was the fall in postoperative serum sodium. Often this fall is of little significance, is readily self-correctable, and does not require the vigorous administration of sodium salts. However, in the patient who has been ill for a considerable time, who has lost much weight, or who has serious hepatic, cardiac, or renal disease, the postoperative fall in serum sodium can be of considerable magnitude. Basically, this would appear to be a dilutional phenomenon, resulting from the administration of intravenous

fluids. Care must be exercised in vigorous "corrective" therapy, as it is potentially dangerous.

It would appear, however, that an x-factor remains that is not understood. This is suggested by the disparity of percentage change in serum sodium and of exchangeable sodium. Furthermore, if you do not give fluids postoperatively, the changes in serum sodium and exchangeable sodium are decreased, but the change in exchangeable sodium is greater than that of serum sodium.

It is entirely possible that certain observed changes in the extracellular fluid volume in response to trauma or operation are iatrogenic. The degree of "expansion" may be importantly related to the amount of parenteral fluid given. Small amounts are observed to permit small increments in "sodium space," and large amounts are followed by relatively larger increases. The reasons for the observed changes in "exchangeable sodium" have not been determined.

# Local Anesthesia and Surgical Training

**DONALD M. GLOVER, M.D., Cleveland**

It is axiomatic that the young general surgeon should be trained in a manner that makes him competent to deal with a wide range of problems, under varying conditions. With the development of anesthesiology to the high plane which is found in most teaching centers, the responsibility of the surgeon for this essential part of the operation is correspondingly reduced. The young surgeon learns to operate in this atmosphere, where he has little volition in the choice of anesthetic agent, and little incentive for taking responsibility in that direction. All too frequently he becomes completely dependent upon talented professional anesthetists of a caliber he may not find available in the community which he ultimately chooses as his professional home. All too frequently he finds himself lost without the help to which he had become accustomed. He then learns, laboriously, what he should have been taught earlier: that much surgery can be done comfortably and safely with local anesthesia alone, and that the use of local anesthesia can make poor general anesthesia better, and good general anesthesia safer.

From the standpoint of surgical training, the employment of local anesthesia provides an ideal discipline. To be successful, the surgeon must have good rapport with his patient and must proceed with gentleness and patience; his powers of observation must be sharpened to the point where he recognizes the first involuntary muscle twitch which signals the need for injection of more anesthetic agent, even before the patient is conscious of pain; he must constantly anticipate the next step in the operation by blocking the field thoroughly to prevent stimulating sensory nerves that cause pain or autonomic fibers that produce hypotension. If he masters the technique of local anesthesia completely, he knows he may prolong the operation with impunity while he develops facility in its performance. The resident soon learns that by substituting local anesthesia instead of deep general anesthesia, for muscle relaxation, he reduces postoperative morbidity, lessens the hazard to the elderly or poor-risk patient, minimizes psychic trauma to the patient, and observes fewer instances of cardiac arrest. He finds that he has more direct control of the patient's status during the operation and he can start operating without waiting for induction of general anesthesia. When working with local anesthesia alone, he observes that there is less bleeding.

As a supplement to general anesthesia, local anesthesia gives the inexperienced surgeon additional dividends. By producing his own muscle relaxation, he makes the anesthesia smoother and often obviates the necessity for deep anesthesia and the use of muscle relaxants. He can learn to work with indifferent general anesthesia, an ability that will often be most helpful to him when he enters practice in a small city, where highly trained anesthesiologists are few or nonexistent.

## General Considerations

### Hazards

Local anesthesia is not without hazard, of course. About 30% of patients operated upon with procaine anesthesia alone show transient hypotension at some time during the procedure. About an equal number ex-

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perience nausea several hours later, and these are not necessarily the patients who have had a period of hypotension. Those who develop hypotension usually do so within 15 to 30 minutes after the procaine has been injected, and the pressure usually returns to normal if the table is tipped into shock position. A few patients will have waves of nausea, which symptom is promptly relieved by breathing oxygen. These effects are less likely to occur when epinephrine is used with the procaine. It has been demonstrated in both animals and man that, when absorbed rapidly into the blood stream, procaine produces vasodilatation, and with very large dosage cardiac function seems to be impaired. In certain very vascular areas the absorption is so rapid that the hazard of hypotension is increased. It was for this reason that epidural (sacral) anesthesia for anal operations was abandoned about 25 years ago. Instead, we now employ local sphincter block for such operations.

### The Anesthetic Agent

There are several satisfactory local anesthetic agents available, but procaine has been shown by animal experiments to be the least toxic of the lot. Some of the others are quicker acting and longer lasting, but it is deemed safer to use the least toxic agent available in the lowest effective concentration. Since procaine hydrochloride, 1%, either with or without epinephrine, has always produced satisfactory anesthesia, higher concentrations are never used. When it seems likely that more than 100 cc. of procaine solution will be required, it is safer to dilute it to 0.5%, and in infants 0.25% solution provides adequate anesthesia.

Epinephrine, when added to the anesthetic solution, more than doubles its duration by slowing absorption, and, in addition, produces a relatively bloodless field of operation. Procaine without epinephrine provides anesthesia which rarely is satisfactory for more than 30 minutes, requiring reinjection after that interval, for a longer operation. For most operations on adults and older children, epinephrine is added in the amount of 0.2 cc. of 1:1000 epinephrine to 30 cc. of 1% procaine hydrochloride, and it is preferred not to exceed a total dose of 1.5 cc. of epinephrine. For operations about the nose and oral cavity, where only small volumes of the anesthetic agent are required and maximum vasoconstriction is desirable, 0.5 cc. of epinephrine per 30 cc. of 1% procaine hydrochloride is used. It is well not to exceed that concentration. For infants the total dose of no more than 0.2 cc. of epinephrine is recommended, although many other surgeons employ much larger amounts. Topical cocaine, although a very effective agent, is never used by me because of idiosyncrasies to the drug which have been observed and have led in occasional instances to cardiac arrest. Regarded as contraindications to the use of epinephrine are hypertension of any degree, known cardiac impairment or arteriosclerosis, thyrotoxicosis, or any history of vasospasm. In one young man with normal blood pressure, but with a history of vascular lability, epinephrine in a total dose of 1 cc. produced marked hypertension and bleeding which was difficult to control.

### "Sensitivity" to Procaine

Many patients give a history of being "allergic" to procaine, on the basis of some disturbing reaction to procaine when used for some minor dental procedure or tumor removal. When investigated, the untoward reaction was thought to have been due to a more toxic agent than procaine, or a relatively large dose of epinephrine. Most have occurred when the operation was performed with the patient in a sitting position. All patients giving such a history are skin tested with several dilutions of procaine prior to operation. In several thousands of patients so tested, no positive skin reaction has occurred, and no reaction has taken place during operation that could reasonably be interpreted as due to sensitivity to the drug. It should not be implied that

intolerance or sensitivity to procaine does not exist, however; it is meant merely that it occurs infrequently, on the basis of our experience.

### Medication

Many patients have been prejudiced against local anesthesia by an unpleasant experience with some minor procedure performed by an inept physician or dentist. For this reason, as well as for synergistic effect, it is usually advisable to give an adequate dose of sedative and a small dose of narcotic preoperatively. Atropine is not used unless one anticipates a combination of local with general anesthesia, because the intense dryness it produces is at times the most unpleasant part of the operation. We have tried various combinations of sedation and narcotics and have never been entirely satisfied with any of them. Our present medication schedule includes, for adults, phenobarbital sodium hypodermically one hour preoperatively and a small dose of morphine, codeine, or meperidine (Demerol) just before the patient goes to the operating room.

During a long operation with local anesthesia—by that we mean two to four hours—the patient often becomes tired, restless, and generally uncomfortable. At this point, the surgeon must decide whether the operation can be completed within another 30 to 45 minutes. If it cannot, it is just as well to have the patient put to sleep with light thiopental (Pentothal) sodium or nitrous oxide and oxygen. Often, however, intravenous morphine is most effective, given slowly in a very small dose (8 mg.). The patient will often relax so completely and quickly that he will drop off to a quiet sleep and remain relaxed and comfortable for the remainder of the operation. It should be borne in mind that all patients operated upon with local anesthesia alone should have a narcotic soon after the operation is completed; otherwise, they may be quite uncomfortable for several hours.

### The Attitude of the Surgeon

Rapport of the surgeon with the patient was mentioned. The attitude of the surgeon toward the patient and toward the operative procedure he is about to perform will determine, in large measure, its success. It scarcely need be stated that any well-adjusted patient is apprehensive about an operation, and an emotionally unstable person may be actually terrified. The emotionally labile patient may, nevertheless, respond equally well to local anesthesia, and may be most enthusiastic about the method after the operation is over. This observation has intrigued me for years. Perhaps the sense of participation and personally surmounting an obstacle is particularly satisfying to such a person. The usual course of the procedure is explained in advance, including the assurance that an intravenous solution will be running continuously in an arm vein and that the anesthetist may add to this thiopental sodium at any moment it is desired by the patient. As the experience of the surgeon increases with this type of anesthesia and he transmits his self-confidence to the patient, the latter will infrequently ask to be put to sleep. If, on the other hand, the surgeon is edgy, insecure, and transmits his *lack* of confidence to the patient, his efforts to work with local anesthesia will fail.

### The Anesthetist's Function

The anesthetist may play an important part in this effort. By making continuous observations of heart rate and blood pressure, he may quickly determine alteration of the status of the patient which may be significant. At the same time, in diverting the patient's attention by conversation, he allays apprehension. This is regarded as a useful exercise for the intern or resident in anesthesiology, but the family doctor may also serve this function effectively. This is sometimes regarded as a boring occupation by residents in anesthesiology, who would prefer to sit in front of a shiny anesthesia machine, manipulating valves

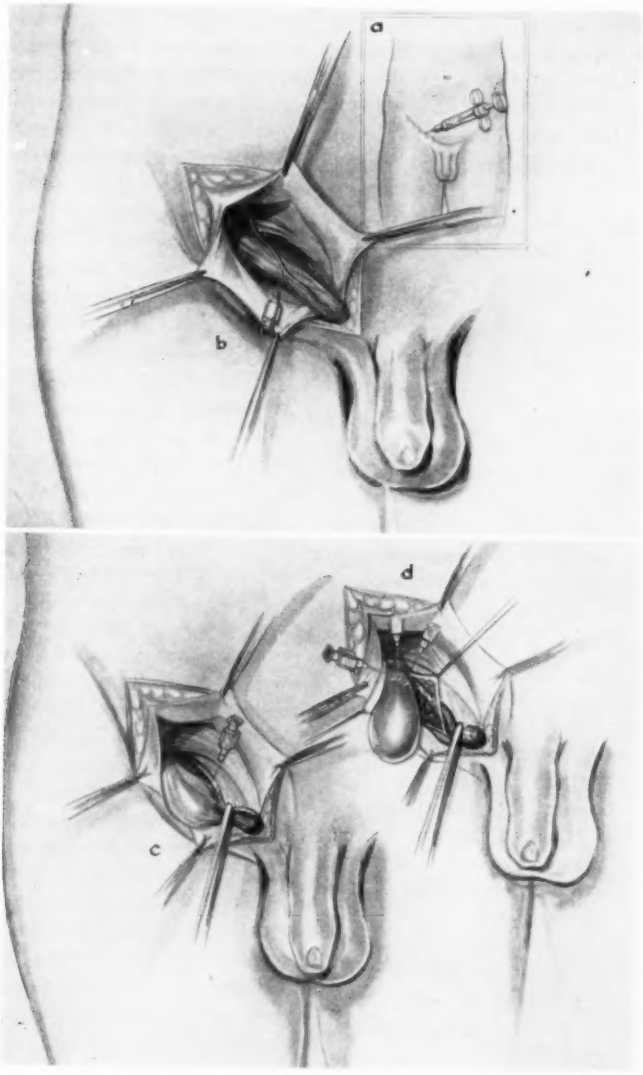



Fig. 1.—Illustrative techniques: local anesthesia in hernia repair. (*a*) Cutaneous infiltration with 1% procaine hydrochloride is made in the line of incision. (*b*) After division of the external oblique aponeurosis, the ilioinguinal nerve is injected directly. (*c*) The vas deferens is identified after lifting the spermatic cord from the floor of the inguinal canal, and procaine is injected into its wall. (*d*) When the peritoneal sac is isolated, its neck is injected with procaine.

and watching the automatic respirator operate: but they may actually learn much about the physiologic changes which take place in the patient during an operation unmodified by general anesthesia. They may also have an opportunity to learn something about the technique of working with light general anesthesia when combined with local. In many situations, the surgeon may work satisfactorily without any anesthetist in attendance, but to have a physician or nurse standing by adds greatly to the com-

fort and safety of the patient. This item is of particular importance with the child or the poor-risk patient.

## Technical Considerations

### Hernia Repair

Hernia repair is the operation which probably lends itself best to the surgical resident as a procedure in which he may perfect his technique, both surgical and in the employment of local anesthesia. As an example, I have chosen an inguinal hernia to demonstrate. A line of coalescing skin wheels is first made to correspond with the planned incision (Fig. 1*a*). A No. 25 short hypodermic needle is satisfactory for the entire procedure. For minimal discomfort to the patient at the outset, it will be found that the introduction of a No. 30 needle will be almost imperceptible. The latter is particularly important when multiple operations need to be done upon a young child and the first "pinprick" is the one most feared. The skin incision is then made, being carried down to the external oblique aponeurosis at the upper (lateral) end of the incision, because at this end there are very few sensory nerves in the fat. Then a little more procaine is injected into the fat at the distal end of the incision, where the cutaneous branches of the ilioinguinal and iliohypogastric nerves fan out. In an obese person, the fat at the latter end of the incision must be cut through gently, watching for delicate nerve fibers that may have been missed by the procaine. Then the filmy layer of areolar tissue is stripped from the external oblique aponeurosis, exposing the external (superficial) inguinal ring. This first part of the operation requires great gentleness, because if the patient is hurt by roughness at this point, his confidence will be shaken and cooperation impaired. A flat director is then slid through the external inguinal ring and beneath the aponeurosis, using great care not to pick up the ilioinguinal nerve, which lies in the areolar tissue and fat directly beneath it, and the aponeurosis is divided in the direction of its fibers. By lifting the two aponeurotic flaps, the ilioinguinal nerve is visualized and injected with a little procaine, where it divides into two branches at the upper end of the incision; the nerve may then be retracted without pain (Fig. 1*b*). The next step is to lift the spermatic cord from the floor of the inguinal canal, by running an empty Penrose drain about it, and to identify the vas deferens, which carries the nerve supply to the testis and cord in its adventitia (Fig. 1*c*). An injection of 2 or 3 cc. of procaine is then made directly into the wall of the vas as far proximally as possible. If an indirect hernia sac is present, this may then be dissected out in the usual manner. When the neck of the sac is approached, a few cubic centimeters of procaine is injected into the peritoneum (Fig. 1*d*). The sac is opened and any contents returned to the abdomen. If it is desired to explore the iliac fossa, more anesthetic agent is injected into the peritoneum about the neck of the sac, in order that retraction will be painless. If the appendix is nearby, it may be lifted out and the mesoappendix injected, in order that it may be removed without pain, which is produced by traction on the mesentery. The sac is then resected and closed securely with an internal purse-string suture. The repair can usually be completed then without any additional anesthesia. Cooper's ligament, the fascia transversalis, and the inguinal ligament contain no pain fibers. The periosteum of the spine of the pubis does, and procaine may be needed there if a suture is to be passed through it. If a direct hernia is present or if the peritoneum needs to be disturbed in Hesselbach's triangle, that also may need to be injected. If the procaine does not contain epinephrine, it may be necessary to reinject the skin before suturing.

The total amount of procaine solution required in this technique should be between 30 and 50 cc. It may be noted that *no* procaine was injected ***beneath*** the external oblique aponeurosis until the latter

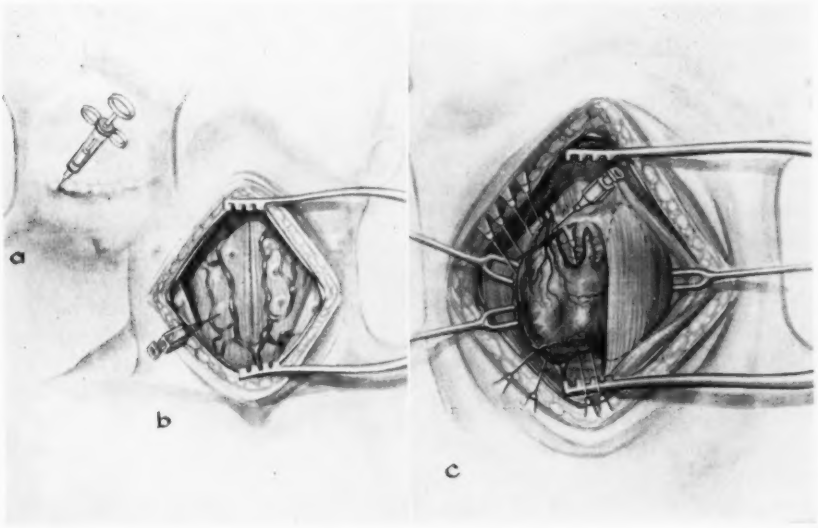
was divided, in order to avoid distending the tissues of the inguinal canal and thus keep from obscuring anatomic structures. The average patient operated upon in this manner will be able to eat the next meal, to be up and about, and to void without difficulty. An occasional patient will be nauseated for several hours, especially if the peritoneum has been manipulated extensively.

### Thyroidectomy

There are certain advantages in performing a thyroidectomy with local anesthesia: (1) The use of an endotracheal tube is avoided, with the attendant danger of vocal cord edema; (2) a long general anesthesia is avoided, especially if the operation consists of total thyroidectomy for carcinoma, and (3) it is very helpful to be able to talk with the patient while dissecting out the recurrent laryngeal nerves. A very satisfactory combination, especially when thyroidectomy is being performed for thyrotoxicosis, is a combination of slow thiopental sodium drip (1 gm. per liter), inhalation oxygen, and procaine without epinephrine.

As shown in the illustration (Fig. 2*a*), the skin is infiltrated in the line of incision, the injection being carried deep enough to include the platysma. The incision is made; the flaps are reflected superiorly and inferiorly, and retractors are placed. The pretracheal muscles are then injected, and the main trunks of the cervical nerves, where they lie at the midpoint of the posterior border of each sternocleidomastoid muscle (Fig. 2*b*). The pretracheal muscles are separated in the midline down to the thyroid capsule; a little procaine is injected into the capsule anteriorly, and the pre-

Fig. 2.—Illustrative techniques: thyroidectomy with local anesthesia. (*a*) The line of incision is infiltrated with procaine, so as to include the platysma. (*b*) After the incision has been made through the skin and platysma, the flaps are freed and reflected superiorly and inferiorly; the pretracheal muscles are then injected as shown, and the main trunks of the cervical nerves are injected where they emerge from the posterior margins of the sternocleidomastoid muscles, about midway between the mastoid process and the sternoclavicular articulation. (*c*) After separating the margins of the pretracheal muscles in the midline and retracting them, the pretracheal fascia is injected to permit elevating the isthmus from the trachea both above and below; the recurrent laryngeal nerve is isolated below the inferior pole, and the superior laryngeal nerve is injected where it lies between the superior thyroid vessels and the thyroid cartilage; the capsule of the gland is injected laterally and posteriorly.



tracheal muscles are retracted from the gland (Fig. 2c). (If the thyroid is obviously the seat of carcinoma, the pretracheal muscles are divided near their attachment to the sternum and reflected, together with the inferior poles, and the dissection of the superior mediastinum is begun.) The superior portion of the pyramidal lobe is then divided and the pretracheal fascia injected anteriorly and laterally to permit elevating the isthmus from the trachea without pain. The pretracheal muscles are retracted or divided, as is found expedient. The superior pole is then isolated, injecting a little procaine into the capsule as the dissection proceeds, and injecting the superior laryngeal nerve where it lies between the medial surface of the superior pole and the lateral surface of the thyroid cartilage. If the gland is not the seat of malignancy, the superior pole is dissected out intracapsularly, after ligating and dividing the superior thyroid vessels, and the lateral surface of the thyroid lobe is dissected down to the inferior thyroid artery. The pretracheal fascia is then injected below the isthmus, and the inferior thyroid veins are divided. The recurrent laryngeal nerve is then identified below the inferior thyroid artery and followed up through the angle of the latter, and along the trachea until the branches enter the thyroid cartilage. The branches of the inferior thyroid artery are then ligated and divided, and the remaining gland is dissected out of its capsule and the isthmus from the pretracheal fascia, preparatory to taking out the other lobe. (If the dissection of the lateral lobe is intracapsular, the recurrent laryngeal nerve is not always dissected out to the thyroid cartilage.) A small portion of one lateral lobe is left attached to the trachea when the gland is free from malignancy.

When thyroidectomy is being performed for carcinoma, the operation is usually done from below upward, the dissection being performed extracapsularly, each parathyroid being isolated with its supplying artery and retained, if not involved. If a deep-chain dissection is done at the same time, the general plan subsequently described is followed. The recurrent laryngeal nerve sometimes absorbs enough procaine to cause a transient vocal cord paresis. The latter usually clears within a few hours.

### Radical Neck Dissection

The deep cervical lymph chain and supraomohyoid dissection starts with infiltration of the line of incision shown in the illustration (Fig. 3). Then the main trunk of the cervical nerve is blocked where it emerges from the midpoint of the posterior surface of the sternocleidomastoid muscle. The incision shown is easy to make, to work with, and to close; and when healed, it leaves minimal scar. Without waiting for the cervical nerve block to become effective, the distal sternocleidomastoid and pretracheal muscles are injected, and the former muscle is divided and retracted upward. The internal jugular vein is ligated and divided, and the lymph node dissection is carried out from below upward in the usual manner, injecting a little procaine in the carotid sheath, the omohyoid muscle, and the carotid bulb, as the dissection proceeds. The upper end of the sternocleidomastoid will now need to be injected, as well as the upper cervical fascia and the tail of the parotid. After the mastoid insertion of the muscle has been divided, the internal jugular vein ligated and divided, and the capsule of the tail of the parotid resected, the external maxillary artery is divided. Then the submaxillary gland capsule, the mylohyoid muscle, the periosteum of the margins of the mandible, and its overlying skin are blocked. The submaxillary glands with surrounding capsule and adjacent digastric and mylohyoid muscles and all lymph-node-bearing tissue may be removed en bloc.

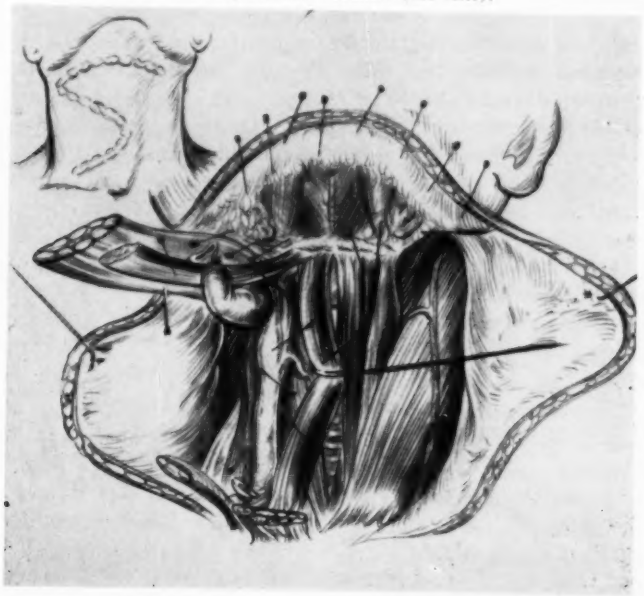
If indicated, the tongue and mandible may be blocked also and removed. This entire procedure can be performed under procaine anesthesia, but is very tiresome for the patient; and before the operation is

over, he should usually have the edge taken off his general discomfort with a small dose of intravenous morphine, thiopental sodium, or gas by inhalation. When the mandible is resected, a tracheostomy should almost always be done; and in some instances it may be safer, when only a portion of the tongue and floor of the mouth is resected, along with the contents of the submaxillary triangles, especially when deep general anesthesia is employed. These procedures are often formidable, because they must be done on elderly patients who are subnormal risks for any operation, and their performance is tedious to both patient and surgeon. The difference in morbidity is considerable between a four-hour endotracheal anesthesia and an operation of similar duration performed with local or a combination of local and light general anesthesia. If one is certain in advance that a tracheostomy will be advisable, it is often an advantage to do it three or four days in advance of the definitive operation. This gives the patient an opportunity to become somewhat accustomed to the tracheal tube, and also gets him past the phase of hypersecretion, which is inevitably present for several days after the tracheostomy is performed.

The deep-chain neck dissection is actually very easy to do with local anesthesia alone. The submaxillary and intraoral parts of the operation are more difficult.

It may be well at this point to comment upon the objection which may be voiced, namely, that local anesthesia should never be used in conjunction with cancer surgery because of the danger that the injection of the local anesthetic may force free tumor cells into the lymphatics or into the general circulation. I have been cognizant of this

Fig. 3.—Illustrative techniques: local anesthesia in radical neck dissection. Insert shows outline of incision, infiltrated with procaine, which I prefer. At the time of the initial injection, the trunk of the cervical nerve is included. The skin flaps are then reflected, with or without the platysma, depending upon the indication for which the operation is being performed. The distal end of the sternocleidomastoid muscle is divided and reflected, together with the omohyoid muscle. The proximal bellies of the homolateral sternothyroid, sternohyoid, and omohyoid muscles are then blocked with procaine to permit retraction. A small amount is also injected into the carotid sheath to permit painless dissection of the internal jugular vein and the common carotid artery. When the carotid bulb (sinus) is visualized, a little procaine is placed directly in its adventitial layer to block the carotid sinus reflex and thus prevent arrhythmia or hypotension. (see text).



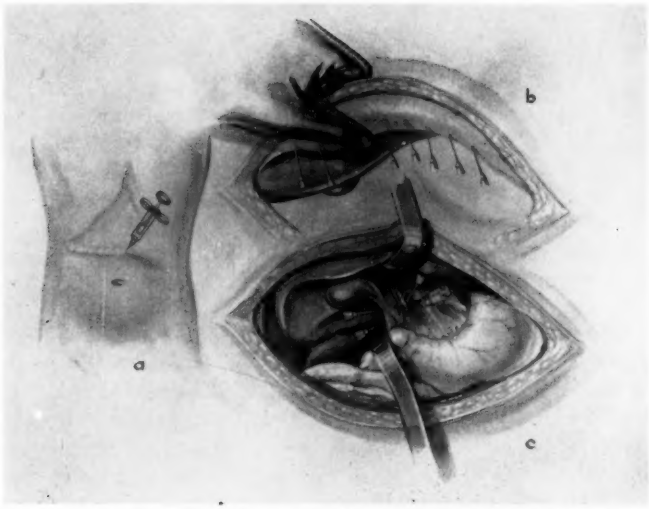



Fig. 4.—Illustrative techniques: local anesthesia in cholecystectomy. (*a*) The right upper transverse incision is outlined with procaine. After the skin incision has been made, the intercostal nerves are injected where they come into the field and the posterior sheath of the rectus is injected. (*b*) When the peritoneum has been incised, its margins are retracted upward and outward to permit thorough blocking of the abdominal wall by procaine. The injections are made 5 to 6 cm. from the peritoneal margins in order to permit retraction. (*c*) After the stomach, duodenum, and hepatic flexure have been retracted, a little procaine is injected just beneath the peritoneum of the porta hepatis to block the delicate branches of the celiac plexus, which fan out in this region. This procedure makes it possible to manipulate the duct system without pain and without reflex muscle spasm and hypotension. If the operation is performed entirely under local anesthesia, additional procaine may be needed in the liver bed and capsule of the gallbladder (see text).

possibility for many years, and, in a long-range follow-up of patients with neoplastic disease, have obtained no objective evidence that the use of local anesthesia has influenced in any manner the incidence of local recurrence or remote metastasis. It is scarcely necessary to state that the surgeon never consciously injects the local anesthetic agent directly into a neoplasm, but it must be admitted that he will occasionally do so without realizing it at the time. It is our conviction that the benefits to the patient with malignant disease of employing local anesthesia far outweigh the slight risk of disseminating tumor cells.

### Cholecystectomy

The description of the use of local anesthesia as an adjunct to gallbladder surgery is now given, illustrating the applicability of the method to the general field of abdominal surgery.

The abdominal wall is prepared and draped, while the anesthesiologist starts electrolyte fluid in a peripheral vein, and makes certain that blood is available and that his equipment is in order to proceed with general anesthesia at any moment. The skin is then infiltrated with procaine in the line of incision, which is then made down to the rectus sheath and aponeurosis of the external oblique (Fig. 4*a*). The muscle wall is then injected, with attention to blocking the intercostal nerves as they come into the field of operation. The incision is then completed down to the peritoneum. While vessels are ligated and skin towels applied, the anesthesiologist puts the patient to sleep slowly. The pertitoneum is then incised and everted, so that procaine may be injected into it, and through it into the overlying muscle far enough from the cut edge to produce relaxation and to permit retraction (Fig. 4*b*). The care with which this is

done determines much of the success of the anesthesia. If the operator wishes to estimate the effectiveness of the method, he may test out the muscle tension before and after injection of procaine just through the peritoneum, then into the muscles surrounding the incision. It is impressive to feel the muscle tension disappear while the injection is being made. By the time this has been completed, the operator can usually make a rapid manual exploration of the entire abdomen, preliminary to retracting the stomach and colon and exposing the porta hepatis and the duct system (Fig. 4*c*). A small amount of procaine is injected just beneath the peritoneum of the porta hepatis and along the gastrohepatic ligament to block the small, interlacing fibers of the celiac plexus. This is a simple and effective means of preventing the reflex, which commonly causes an abrupt blood pressure drop when traction is exerted upon the common bile duct, with the patient lightly anesthetized. If the duct dissection has already been started without the procaine injection, and the blood pressure has already dropped, the pressure will return to normal quickly when procaine is injected as described.

The cystic artery and cystic duct may now be isolated and ligated and operative cholangiography carried out. While the films are being developed, the gallbladder may be dissected out from its capsule in the liver and the latter sutured. The appendix can usually be delivered easily into the incision, and if the cholecystectomy has been uncomplicated, this is done, the mesoappendix injected with procaine, and the appendectomy performed in the manner preferred by the surgeon. If the cholangiograms are negative, the abdomen may be closed. It may be found necessary to reinject the peritoneum and muscle wall with procaine, in order to make closure easy. As soon as the peritoneum is closed, the general anesthesia is discontinued completely. The muscle wall, subcutaneous tissue, and skin can be sutured without difficulty, even when the patient is straining, provided that a transverse incision has been employed.

What are the advantages of this application of local anesthesia to an abdominal operation? Our answers are as follows: (1) reduction of general anesthesia time by 20 to 30 minutes; (2) lessened depth of general anesthesia and avoidance of muscle-relaxing drugs, other than procaine; (3) virtual elimination of pulmonary complications; (4) lessened incidence of gastrointestinal dysfunction after operation (gastric suction is infrequently necessary); (5) less electrolyte and nutritional depletion; (6) smoother postoperative course for the patient.

### Other Operations

The same general plan of application of local anesthesia may be used in other abdominal operations. Even if the surgeon employs only the peritoneal and muscle-blocking part of the procedure, he will find this helpful. The performance of extensive abdominal operations with local anesthesia alone is not advocated, but it will be found a very useful "ace in the hole" when it is necessary to do a gastrectomy or colon resection for carcinoma on an elderly patient, or on other patients who present serious vascular or pulmonary complications. We have performed extensive resections upon patients in their 90's entirely with local anesthesia. With patience and gentleness this can be accomplished without undue difficulty to patient or surgeon.

Two other type operations are mentioned as illustrations, both of which may be considered as controversial from the standpoint of employment of local anesthesia: mastectomy in the adult, and abdominal operations in the newborn.

First, we can consider local anesthesia as an aid to the operation of radical mastectomy. When the presumptive diagnosis is benign tumor of the breast, an incision is made just outside the margin of the areola and for about half its circumference, in the appropriate portion of the breast, since there

seems no justification for grossly deforming the breast in order to remove a harmless lump. The line of incision is infiltrated with procaine; then the breast tissue is infiltrated widely about the suspected tumor, avoiding the lesion itself. The entire nodule is then resected and the incision closed. The entire block is sent for frozen-section examination, while the incision is being sutured. If the operator has been fairly certain that the lesion is malignant from the start, he may prefer a more direct approach to the lesion, rather than the periareolar incision.

If the frozen section shows the nodule to be malignant, the surgeon explains to the conscious patient that it is necessary to remove the involved breast and reassures her concerning the outcome. While general anesthesia with intravenous thiopental sodium and gas by inhalation is being induced, the field of operation is reprepared and redraped. The field is blocked with procaine, outlining the incision the surgeon prefers; the lateral branches of the intercostal nerves are blocked in the axillary portion of the field, and the distal branches where they penetrate the pectoralis major near the sternal margin. Thus, the surgeon can make the incision without delay and proceed with the operation. By reenforcing the local anesthesia from time to time, when breathing or movement of the patient denotes sensory stimulation, the long procedure may be carried out with very light anesthesia, and she may be nearly awake as the dressing is applied.

The morbidity from excision biopsy followed by radical mastectomy, with or without internal mammary dissection, under conventional deep general anesthesia of three to four hours' duration, is considerable. Such patients are often nauseated and unable to retain food or fluid for two or three days after the operation. After an operation performed with the combination of local and very light general anesthesia, the patient is frequently ready for a light meal by the evening of operation, and practically always by the following morning, and is then able to be out of bed with relative comfort.

Abdominal operations may be performed upon the newborn or young infant satisfactorily with local anesthesia alone, or with local and just enough open-drop ether anesthesia to keep the baby from moving about, a fact that is of great comfort to the young surgeon, who finds himself in a small city with limited help.

## Summary

The place of local anesthesia in the surgical armamentarium is discussed from the standpoint of the operator and that of the patient.

Methods of application, anesthetic agents, dosage, and potential hazards are described.

Outlined are illustrative operative procedures wherein local anesthesia alone or in conjunction with general anesthesia may be helpful.

## Conclusions

The surgical resident should acquire, as part of his training, competence and confidence in the use of local anesthesia, both alone and in combination with other anesthetic agents.

Such training permits him greater flexibility in anesthetic procedures, time to operate deliberately and accurately, and peace of mind when he is called upon to operate where general anesthesia of high order is not available. To his patient, also, are granted greater safety and postoperative comfort.

Mr. William M. Holmes, Medical Illustrator, St. Luke's Hospital, supplied the illustrations.

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## DISCUSSION

DR. ROBERT M. ZOLLINGER, Columbus, Ohio: There are two reasons for my being here. In the first place, Dr. Glover was kind enough to ask me to discuss his paper, and, in the second place, I felt rather guilty after reading his manuscript, for I was not instructing my residents in the art of anesthesia. He has demonstrated a beautiful

technique in his slides. We could use an artist of that caliber in Columbus.

As the author has pointed out, I suspect to a large extent, local anesthesia is a lost art, and every young surgeon should become skilled in its use. I confess that I have not used it very often in recent years, and I am sure that few young surgeons are skilled in this particular aspect of anesthesia.

This is in contrast to the situation when we were interns, when most of us owned a book known as "Regional Anesthesia: Its Technic and Clinical Application," by Gaston Labat. Not only was it good on local anesthesia, but it provided a review of anatomy. After we had studied this particular technique of local anesthesia, points of anatomy which might otherwise have been missed became clear. I looked through my copy not long ago, and I must say it is more or less a collector's item as far as I personally am concerned.

I don't think I should be inclined to use local anesthesia in many of the types of operations that Dr. Glover has prescribed. However, I suspect we might use it more frequently in the repair of hernias. Certainly, we might be a little gentler and approximate the tissues with less tension. I have tended to advise that we keep the use of curare to a minimum when we are using general anesthesia in the repair of hernia.

I should like to emphasize two other points in the use of local anesthesia. On occasion I have seen toxic reactions occur even with the use of procaine, and I think young surgeons should remember to have intravenous thiopental (Pentothal) or a drug of that type available, and they should know the early symptoms of toxicity. If you are going to use 0.5% procaine hydrochloride, you don't have to worry much about it.

Second, before the war we were never allowed to use epinephrine, mainly for the reasons Dr. Glover mentioned. I think our chief felt that wounds would be a little bloody as the epinephrine wore off.

Although learning to work under local anesthesia is time-consuming and tedious for the young surgeon, the effort will be more than repaid when he finds himself in a tight spot, without the help of a skilled anesthesiologist, as Dr. Glover mentioned.

Lastly, it might be well if all of us used local anesthesia once in a while in hernia cases to show how rough we have become. We might be a little gentler in the future—no question about it. I don't believe our anesthesiologists would object too much, for I suspect they felt that we would miss them so that we would promptly return to general anesthesia.

DR. CHARLES E. HOLZER JR., Gallipolis, Ohio: I want to second Dr. Glover's and Dr. Zollinger's remarks. I have continued to employ local anesthesia for inguinal hernia, primarily for my own discipline and for that of my assistants and nurses in teaching the need for gentle retraction and careful handling of tissues.

I want especially to comment on the use of intercostal nerve block in upper abdominal surgery. We have employed a different technique from Dr. Glover's, using bilateral intercostal nerve block, blocking the lower eight intercostal nerves on each side, with 1% Cyclaine, or hexylcaine. This drug also has a very low toxicity.

We became interested in the use of intercostal nerve block while looking for a better anesthetic for poor-risk patients. We started using various agents and came upon hexylcaine, which has proved to be very satisfactory. The results were so good that my colleagues and I have started using intercostal nerve block almost exclusively in upper abdominal surgery, usually in connection with light general anesthesia or small doses of meperidine (Demerol) given intravenously. Until last week we had had experience with 284 cases in which no toxic effects or complications were attributable to the block alone. Although we have not completed a careful analysis of the series, we are definitely of the opinion that our postoperative complications are fewer.

The things we have been able to "get away with," so to speak, with this type of anesthesia have led our internists to ask us to do surgery in cases of almost impossible risk, and sometimes it is a little difficult to convince them that occasionally one just cannot operate on these patients.

In this series of patients we had 32 who were classified as extreme-risk patients, owing to extreme old age, cardiac failure, myocardial fibrosis, shock, and so on, and all 32 of these had major intra-abdominal operations. There were only six deaths. The mortality was 18.4%. There were no deaths on the operating table or in the first few postoperative hours.

We feel, therefore, that this method is a very valuable adjunct, and, as a matter of fact, we have practically eliminated the use of muscle relaxants, particularly curare, in our service. We feel that the use of curare should be kept to a minimum, and the use of the intercostal nerve block has enabled us to do so.

DR. WILLIAM O. MCQUISTON, Peoria, Ill.: Contrary to what one might expect, we anesthesiologists do not take exception to the surgeon's use of local anesthesia. In fact, we think it should be used much more frequently. We would suggest that regional block might make a little nicer anesthesia than the direct local anesthesia, but in many situations—for instance, in operations around the head and neck—in emergencies such as a Colles fracture with a full stomach or hand injuries, and even in such operations as hemorrhoid-

ectomy, the procedure can be more safely done under regional or local anesthesia.

Many of the so-called reactions to procaine are due not to procaine but to epinephrine, and so we usually advise against epinephrine. Scopolamine, added to the morphine for premedication, will add a little amnesia, which is appreciated by the patient. Lidocaine (Xylocaine) is one of our newer agents which has tremendous spreading properties, and, in using lidocaine it is necessary only to get close to the nerve, not really on it.

Dr. Daniel Moore has published two books recently on block anesthesia, which should be in every surgeon's library.

Dr. Robert Whittlesey, Cleveland: If you will pardon me for arising twice in the short space of three hours, I should like to comment on this paper by Dr. Glover.

Dr. Glover talks so rapidly and packs so much technical "meat" into a short space of time that one tends to forget the original thought which lay behind the preparation of his paper. But it is typical of papers by Dr. Glover, who has spent years and has given of his time generously and unstintingly in the training of surgical residents.

Dr. Glover and I were talking about this paper, after I had read the abstract, on the train coming to Columbus last night, and I was about to take issue with some of the things that I expected Dr. Glover would say but which he did not say. Thinking the matter over after our discussion, I believe that in large-city practices we all too easily get into the habit of letting the whole matter lie in the hands of the anesthesiologist. When one considers the case of the surgeon who is called upon to operate in smaller—often rural—communities, frequently miles from his usual place of work, and all too often far away from adequate nursing care and from well-trained anesthesiologists, one does realize the importance of what Dr. Glover has presented this afternoon.

Dr. Donald M. Glover, Cleveland, Ohio: I thank the discussants for their remarks.

One point about the toxic reaction that Dr. Zollinger mentioned briefly: It is true that there is a great deal of feeling against the local anesthetic agents because so many persons think they are sensitive to, or, as they put it, allergic to, procaine or some other local anesthetic agent. All such impressions have to be taken at face value. We have done literally thousands of skin tests on thousands of patients using procaine, and up to now I have not found anyone who had anything that could be classified as a sensitivity reaction, nor have I seen any effect from its use which could be categorized as a sensitivity reaction. However, I feel very strongly that there are some persons who have the capacity to react abnormally, and we have to use great caution.

Dr. Holzer certainly is to be congratulated on the excellent results he has shown. I, too, believe that the intercostal block technique is excellent, and it probably has advantages over the type of field block that we perform, but is a little more complex. I have found that the field block is handier for me, but I am sure that for many operators the intercostal block will work better.

It is true that some agents, like hexylcaine, and certainly lidocaine, are more effective than procaine. We have been very conservative and use procaine only. Some of the other agents are perfectly safe in small amounts, but there is no question that they are more toxic than procaine, as has been shown by animal work.

Dr. McQuiston mentioned scopolamine, which truly is a helpful agent in conjunction with local anesthesia. We have found its action somewhat unpredictable, and some people get peculiar reactions from it; so, in general, we have avoided its use.

# Early Excision of More Than Twenty-Five Per Cent of Body Surface in the Extensively Burned Patient

*An Evaluation*

**BRUCE G. MacMILLAN, M.D., Cincinnati**

Although the survival time of extensively burned patients has increased, modern advances in therapy have not appreciably decreased the mortality rate in this group of patients. If the per cent of area burned for 412 patients treated between 1952 and 1956 is plotted against the per cent mortality, it is noted that a 55% total body burn is associated with a 50% mortality rate, represented by the solid curve (Fig. 1). This experience differs little from the mortality rate reported by Bull and Fisher for 967 cases treated between 1948 and 1952, where a 50% total body burn was associated with a 50% mortality rate, represented by the broken curve (Fig. 1).

The influence of infection upon the mortality rate is clearly defined when the causes of 86 deaths occurring between 1950 and 1956 at the U. S. Army Surgical Research Unit are analyzed (Fig. 2). Of the 86 deaths, 50 resulted from invasive infection or septicemia. In addition to the 50 deaths resulting from septicemia, there were 10 proved cases of septicemia that survived.

The organisms isolated from this group of patients and their antibiotic sensitivity patterns are shown (Fig. 3). Micrococcus pyogenes was recovered in 65% of the cases and found to be sensitive to chloramphenicol (Chloromycetin), bacitracin, erythromycin, and novobiocin (Cathomycin). Pseudomonas and Proteus were recovered

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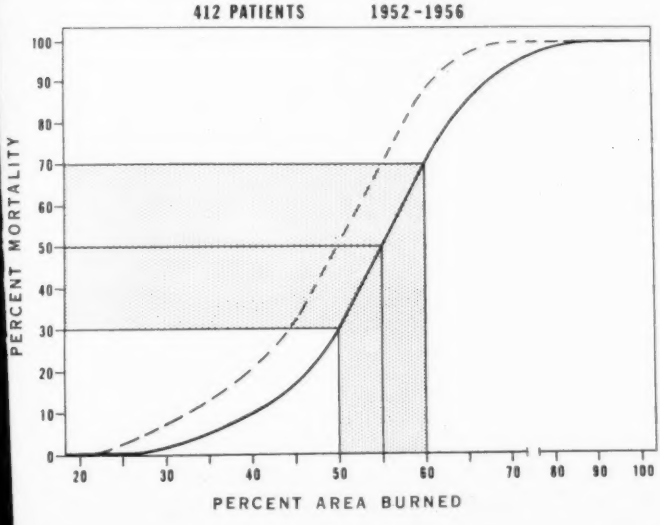



Fig. 1.—Burn mortality rate of 412 patients treated at the U. S. Army Surgical Research Unit between 1952 and 1956 (solid curve). Burn mortality of 967 patients reported by Bull and Fisher, treated between 1948 and 1952 (broken curve).

| CAUSE | CASES | MEAN % BURN TOTAL | MEAN % BURN 3rd° | MEAN DAY OF DEATH |
|---|---|---|---|---|
| • SEPTICEMIA | 50 | 60 | 40 | 21 |
| • Fluid Imbalance | 10 | 72 | 58 | 5 |
| • Incineration | 6 | 86 | 81 | 1.8 |
| • Pulmonary Damage | 5 | 42 | 29 | 0.7 |
| • Curling's Ulcer | 3 | 58 | 22 | 22 |
| • Others | 12 | | | |

• Hepatitis • Pneumonia • Cardiac arrest
• Myocardial infarction • Cerebral contusion

Fig. 2.—Causes of death in 86 patients occurring between 1950 and 1956 at the U. S. Army Surgical Research Unit.

in 35% and 20% of the cases, respectively, and were found to be sensitive to polymyxin and chloramphenicol.

Despite all 60 patients being treated with this specific antibiotic therapy, only 10 survived (Fig. 4). Those patients who died had a mean total body burn of 60% and a mean area of third-degree burn of 40%, as opposed to a mean total body burn of 40% and a mean area of third-degree burn of 20% in those patients who survived. The mean date of onset of septicemia was the 11th postburn day, and the mean day of death due to septicemia was the 21st postburn day.

When the interval between burning and the initial postive blood culture is plotted for this group of patients, a precipitous rise in the number of positive blood cultures is noted on the fifth postburn day (Fig. 5). If the areas of full-thickness burn harboring these bacteria could be removed prior to this period of invasion and the resulting wound closed with skin grafts, the hazards of septicemia might be circumvented.

## Method

In September, 1955,[1] an evaluation was planned to test this hypothesis. Cases were selected on the basis of an unexpected mortality rate of 50% (represented by the shaded area in Figure 1). Subjects studied ranged from 5 to 55 years of age. Patients included had a burn index (third degree, also one-half second degree) in the range of 35 to 60, with 25% or more of the body surface involved in full-thickness burn. The patients admitted after the fifth postburn day were treated by conventional methods, and those admitted prior to this time

| ORGANISM | PERCENT CASES | SENSITIVITY |
|---|---|---|
| • Micrococcus pyogenes | 65 | C B E Ca |
| • Pseudomonas | 35 | Px |
| • Proteus | 20 | C |

Figure 3

Fig. 3.—Organisms isolated in 60 proved cases of septicemia at the U. S. Army Surgical Research Unit between 1950 and 1956 and their antibiotic sensitivity patterns. *C* indicates chloramphenicol (Chloromycetin); *B*, bacitracin; *E*, erythromycin; *CA*, Cathomycin, and *Px*, polymxin.

| RESULTS | CASES | MEAN PERCENT TOTAL | MEAN PERCENT 3rd° |
|---|---|---|---|
| • Deaths | 50 | 60 | 40 |
| • Survivors | 10 | 40 | 20 |

Mean day of onset — 11th postburn day
Mean day of death — 21st postburn day

Figure 4

Fig. 4.—Burn deaths and burn survivors with proved septicemia treated at U. S. Army Surgical Research Unit between 1950 and 1956.

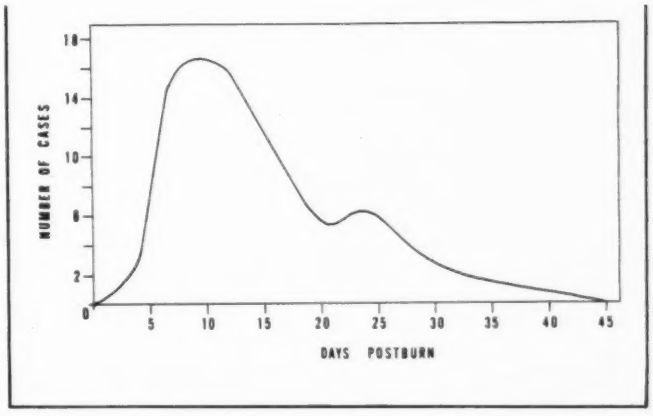



Fig. 5.—The interval between burning and initial positive blood cultures for 60 proved cases of septicemia treated at the U. S. Army Surgical Research Unit between 1950 and 1956.

were included in the excisional group. All confluent areas of full-thickness burn involving at least 25% of the total body surface were excised. This was done in one or two stages between the second and the fifth postburn days. Autograft and/or homograft coverage was performed immediately or 48 hours after excision.

The extent of excision was determined by the patient's ability to discriminate sharp pinprick. When possible, adjacent questionable areas of full-thickness burn were included in the area of excision to ensure primary wound healing. All areas were excised down to the underlying superficial fascia. Two or more surgical teams were

Fig. 6.—*A*, patient E, showing a confluent area of full-thickness burn over trunk and upper extremities which involves 36% of the total body surface.
*B*, burned area after excision down to the underlying superficial fascia.
*C*, initial skin coverage with autografts and homografts. Homografts cover the right anterolateral chest wall.
*D*, complete autogenous skin coverage, accomplished on the 30th postburn day.

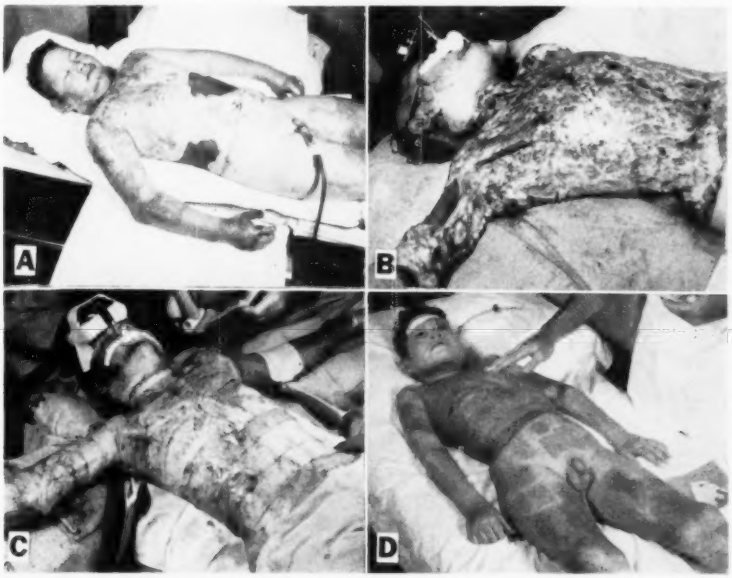


TABLE 1.—*The Use of Homografts in Five Patients Treated by Early Excision*

| Patient | Burn Extent | | Excision, Per Cent | Initial Coverage, Per Cent |
|---|---|---|---|---|
| | Total | 3d | | |
| A | 43 | 31 | 30 | 100 |
| B | 45 | 30 | 30 | 50 |
| C | 55 | 43 | 33 | 90 |
| D | 45 | 30 | 30 | 20 |
| E | 45 | 36 | 36 | 10 |

TABLE 2.—*The Use of Homografts Treated by Early Excision of Extensive Areas of Full-Thickness Burns*

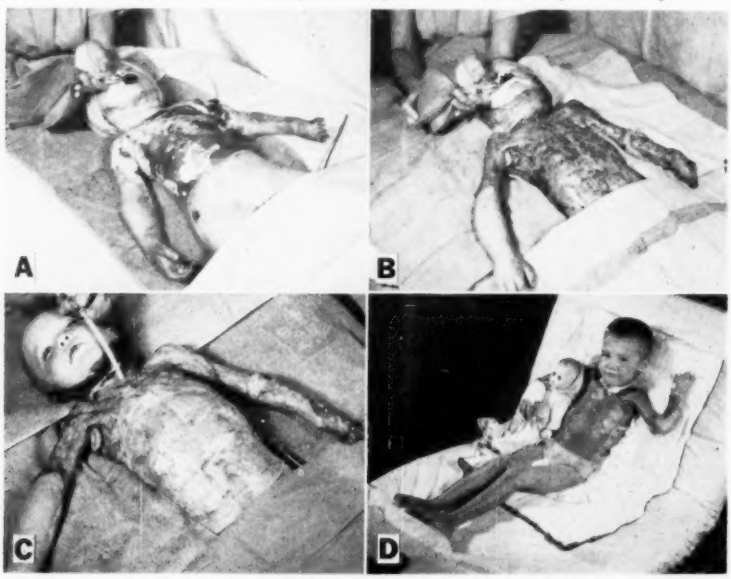
| Patient | Burn Extent | | Excision, Per Cent | Initial Coverage, Per Cent |
|---|---|---|---|---|
| | Total | 3d | | |
| F | 70 | 46 | 30 | 50 |
| G | 54 | 40 | 35 | 80 |
| H | 50 | 45 | 40 | 90 |
| I | 65 | 50 | 40 | 70 |
| J | 61 | 58 | 50 | 80 |

required to keep the operative time under two hours for each procedure. During the immediate postexcisional period a definite clinical improvement was noted in all patients. An interval of 48 hours was usually allowed between the excisional procedure and the application of grafts. All remaining unburned skin was utilized for autografts at the time of the first grafting procedure. Homografts were used to complete the initial skin coverage. The period of protection afforded by the homografts varied from two to four weeks.

A confluent area of full-thickness burn involving 36% of the total body surface in Patient E is shown in Figure 6*A*. The extent of the area excised down to the underlying superficial fascia is shown in Figure 6*B*. Initial skin coverage was accomplished 48 hours after the excisional procedure with autografts and homografts. Homografts accounted for 10% of the initial skin coverage and were placed over the right anterolateral chest wall (Fig. 6*C*). Complete autogenous skin coverage was accomplished on this patient's 30th postburn day (Fig. 6*D*).

The important role played by homografts as an effective method of temporary wound

Fig. 7.—*A*, patient H, showing a confluent area of full-thickness burn over torso and upper extremities which involves 45% of the total body surface.
*B*, the burned area after being excised down to the underlying superficial fascia.
*C*, initial skin coverage with 90% homografts. The autografts are located in both axillae.
*D*, complete autogenous skin coverage, accomplished on the 37th postburn day.



closure until additional skin can be obtained from either healed donor sites or healed areas of partial-thickness burn becomes apparent when their use in the first 10 cases is reviewed.

In the first group of five patients (Table 1) the extent of excision ranged from 30% to 36% of the total body surface. Initial coverage with homografts ranged from 10% to 100% of the grafted area. In the second group of five patients (Table 2) the extent of excision ranged from 30% to 50% of the total body surface. Initial coverage with homografts ranged from 50% to 90% of the grafted area.

A graphic demonstration of the lifesaving value of homografts is demonstrated in Patient H, who sustained full-thickness burns of her torso and upper extremities which involved 45% of her total body surface (Fig. 7*A*). This area was excised down to the superficial fascia on the patient's second postburn day (Fig. 7*B*). Because of limited donor sites at the initial grafting procedure, only 10% of the excised area could be covered with autografts, and the remaining 90% of the excised area was covered with homografts. Autografts were placed in both axillae (Fig. 7*C*). Complete skin coverage with autografts was accomplished on this patient's 37th postburn day (Fig. 7*D*).

## Results

Since September, 1955, this study has included 22 patients, 14 patients being treated by early excision and 8 patients being treated by conventional methods. Two of the eight patients treated by conventional methods survived. Initial grafting in these two patients was started on the 32d and 24th postburn days, respectively. Autogenous skin coverage was completed on the 90th and 135th postburn days, respectively. The remaining six patients developed septicemia between the 7th and the 26th postburn day and died of septicemia between the 11th and the 73d postburn day. The mortality rate in the group treated by conventional methods was 75%.

TABLE 3.—*Excisional Group of Fourteen Patients*

| Cases | Survivors | Deaths | Causes of Death |
|---|---|---|---|
| 1-5 | 2 | 3 | Septicemia<br>Pulmonary infarction<br>Accidental |
| 6-10 | 3 | 2 | Septicemia<br>Curling's ulcer |
| 11-14 | 3 | 1 | Septicemia |
| Mean day of coverage | | 40th postburn day | |
| Mortality rate | | 42% | |

The 14 patients treated by early excision have been divided into three groups. The number of survivors, deaths, and causes of death are shown in Table 3. In the first group, of five patients, there were two survivors and three deaths. Complete autogenous skin coverage was accomplished in the two survivors on the 30th and 37th postburn days, respectively. The three deaths in this group resulted from septicemia in one patient, who died on the 33d postburn day, from a pulmonary infarction in one patient, who died on the 42d postburn day, and from an accidental death in one patient, who died on the 33d postburn day.

In the second group, of five patients, there were three survivors and two deaths. Complete autogenous skin coverage was accomplished in the three survivors on the 39th, 42d, and 38th postburn days, respectively. The two deaths in this group resulted from septicemia in one patient on the 10th postburn day and from a Curling's ulcer in one patient on the 37th postburn day.

In the third group, of four patients, there were three survivors and one death. Complete autogenous skin coverage was accomplished in these three patients on the 31st, 35th, and 54th postburn days, respectively. The one death in this group resulted from septicemia on the 34th postburn day.

## Summary and Conclusions

The mortality rate in the excisional group of patients was 42%, as compared with a mortality rate of 75% in the group of patients treated by conventional methods. The

mean day of complete autogenous skin coverage for the excisional group was the 40th postburn day, as compared with the 90th and 135th postburn days for the two patients who survived in the group treated by conventional methods.

While the 14 cases here presented are too small a series from which to draw definite conclusions, certain pertinent observations can be made.

1. Surgical stress of the magnitude described has been well tolerated and has resulted in no operative deaths.

2. Removal of areas of full-thickness burn involving 25% or more of the total surface has resulted in a temporary improvement in the patient's general clinical condition.

3. Homografts have been used effectively as a method of temporary wound closure.

4. The shortened period between burning and complete autogenous skin coverage has resulted in a marked decrease in postburn morbidity.

5. The incidence of septicemia has been influenced by early removal of large areas of full-thickness burn.

6. Experience with this method of treatment gained to date justifies its further critical evaluation.

Cincinnati General Hospital, Dept. of Surgery (29).

## REFERENCE

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## DISCUSSION

DR. WILLIAM REQUARTH, Decatur, Ill.: In the last 10 to 15 years one of the main advances in the treatment of burns has certainly been early excision of the eschar. Dr. MacMillan and Dr. Altemeier have carried it much further and have excised burns immediately, before the formation of eschar.

I should think a serious criticism of this method would be the inadvertent excision of part-thickness burn. I should like to ask Dr. MacMillan, therefore, how he determines what areas are full-thickness. My experience has been that the determination of the thickness of a burn is usually done in retrospect, unless it is done at least by the 9th, 10th, or 14th postburn day.

We learn only by evaluation of new methods. Certainly, immediate surgical excision of flame burns, as outlined by Dr. MacMillan, is experimental and hazardous for the patient except in expert hands.

I would like to show a few slides illustrating some of the aspects of excisional therapy of electrical burns. In these cases the burn eschar was obvious after a few days, as is characteristic of electrical burns.

(Slide) This patient had a combination of electrical and flame burns, rather extensive. The excisional therapy was started on the 10th or 11th postburn day.

(Slide) This shows the initial dressing, when we were able to delineate more accurately the areas of third-degree burn.

(Slide) This is just prior to excision.

(Slide) This is a full-thickness electrical burn of the palm. I want to make one strong point about excision of electrical burns. After excision of the eschar several days should elapse before the area is covered with a graft. Frequently further necrosis occurs, even several days after excision. This would result in loss of the graft if put in place immediately after excision.

(Slide) This shows a burn of the palm and thumb.

(Slide) This slide shows the graft that was applied over the palm, and also the flap that was placed over the exposed bone.

(Slide) This is an electrical burn of the plantar surface of the foot, which was excised three or four days afterward and covered with a thick split graft. As you know, plantar skin differs from that in other parts of the body, and very often a flap is required. However, it certainly is worth while to try a thick split graft before one goes through all the surgical difficulties of transferring a flap into this area.

DR. WILLIAM A. ALTEMEIER, Cincinnati: In patients with extensive devitalized areas of skin produced by thermal injury, one can expect the areas to act as a nidus for developing infection, which, in turn, permits the invasion of the physiologic interior by bacteria, with the development of cellulitis, septicemia, metastatic lesions, prolonged morbidity, or death.

I don't think there is any question that infection is the chief unsolved problem in the management of patients with burns. Dr. MacMillan's experimental project was started at the Research Unit at Brooke Army General Hospital, under the sponsorship of the Navy and the National Research Council. It has been continued at the Cincinnati General Hospital.

The project was initiated as an experimental method of removing, by surgical excision, the devitalized skin before it could act as a source of infection and distribution for bacteria to produce a septicemia.

While the preliminary results of Dr. MacMillan's study are very encouraging, I would like to emphasize that this is still an experimental method which is not ready for general use. These burn patients are ill; they require close supervision and intensive supportive therapy.

Many surgeons, both military and civilian, are interested in the results of this problem and the inferences that can be drawn from it. Help is needed in the management of patients who have third-degree burns of more than 25% of the body, and we hope that Dr. MacMillan's work will provide us with some of the answers to this unsolved problem.

DR. BRUCE G. MACMILLAN, Cincinnati: I do not know, nor do I think anyone else knows, exactly how to determine the extent of an area of third-degree burn. When this project was started, we tended to underestimate the area of third-degree burn. As a result, we tended to be too conservative and not to excise the burn area widely enough. Areas of deep second-degree and third-degree burn were left behind, which defeated to a certain extent the basic purpose of this project, namely, to convert the early burn to a healed wound.

At the present time, if there is any question concerning the area of third-degree burn, the tissue is included in the burn area excised. By this means the burn wound can be converted to a clean wound. If areas of deep second-degree or third-degree burn remain, the graft take is jeopardized. Since so much is at stake, once the decision has been made to remove these large areas, we feel that it is absolutely necessary to take such measures.

The method of differentiating second-degree burns and third-degree burns is done by the patient's ability to discriminate sharp pinprick. We realize the limitations of this method but, after repeated attempts in the first 48 hours, we feel fairly confident in our ability to determine the absolute area of full-thickness burn.

# Reconstruction of Upper Gastrointestinal Tract with Colon Segments After Esophagogastrectomy

WILLIAM E. NEVILLE, M.D., and GEORGE H. A. CLOWES Jr., M.D., Cleveland

Dissatisfaction with the established methods of reestablishing intestinal continuity following esophagogastrectomy or total gastrectomy has led to a search for improved methods. The operation designed for complete eradication of malignant disease results in postoperative morbidity. Inability to eat normally renders adequate nutrition difficult, owing to lack of a food reservoir.

Our satisfaction with the use of the colon as an esophageal substitute [13] led us to investigate the use of this portion of the bowel to replace the stomach.

It is the purpose of this paper to present observations on 12 patients in whom a portion of the transverse colon has been used to establish esophagoduodenal continuity following esophagogastrectomy and total gastrectomy.

## Operative Technique

Preoperative preparation consisted of restoration of nutrition and chemical balance and sterilization of the colon. The former was generally accomplished by tube feeding and intravenous electrolyte administration. The colon was prepared for two to four days with neomycin (1 gm. every six hours by mouth) and cleansing enemas.

The operations were performed with the patient in a semisupine position and the left side elevated to 45 degrees. In the majority of instances two operative teams were employed. The abdomen and chest were opened simultaneously through either a left thoracoabdominal incision or separate thoracic and abdominal incisions. The lower esophagus, spleen, and entire stomach were mobilized to remove the cancer. The spleen was removed with the specimen in each instance, the tail of the pancreas being included in six patients. The lymph nodes of the celiac axis were resected as completely as possible. The transverse colon was mobilized from the hepatic to the splenic flexure. A portion of the bowel was separated proximally and distally. The mesentery was divided down to the origin of the middle colic artery and vein, leaving the segment of the colon suspended upon a vascular pedicle. The proximal end was anastomosed to the lower esophagus and the distal end to the remaining portion of the stomach or the duodenum. In three patients it was implanted in an antiperistaltic fashion, and end-to-end colocolostomy was performed. If a portion of the stomach remained, a tube gastrostomy was done; otherwise, a tube jejunostomy was inserted. These tubes were put on suction during the first few days, obviating the necessity of a nasogastric tube, and serving subsequently for feeding purposes. These tubes were removed when oral feedings were reinstituted.

Submitted for publication March 28, 1958.

Read at the 15th Annual Assembly of the Central Surgical Association, Columbus, Ohio, Feb. 21, 1958.

## Results and Complications

To date the transverse colon has been used to establish esophagoduodenal continuity in 12 patients for malignant disease. Three patients died of complications in the early postoperative period. An additional three patients have died of progression of their disease. At the moment six patients are living, from 6 to 72 months after operation.

Two patients died on the 7th and 10th postoperative days, respectively, of pneumonia. Postmortem examination showed intact suture lines. Another, an elderly man died of an empyema due to a mixed colon bacillus and Streptococcus infection. By mistake, his colon was not adequately prepared. He failed to receive neomycin. Within 48 hours a fulminating infection developed in his left chest. Postmortem examination, nearly three weeks later, disclosed partial disruption of the esophago-

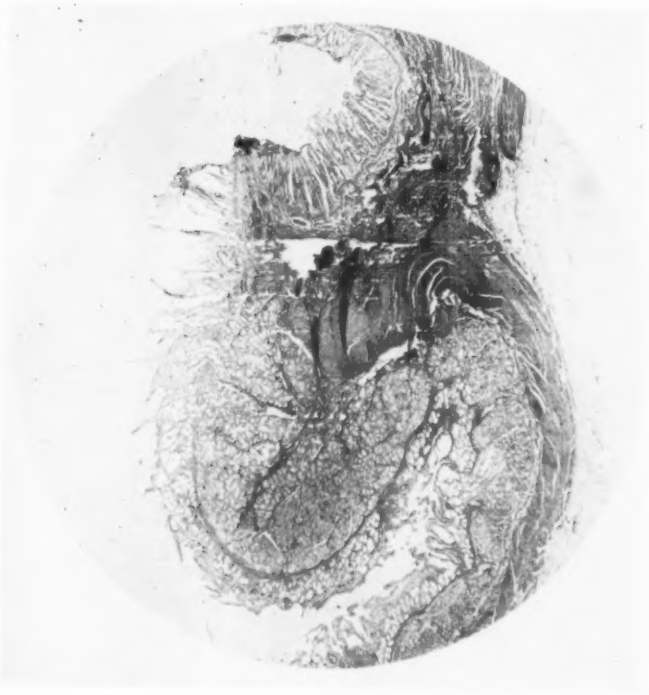

Fig. 1.—Microscopic examination of the colo-duodenal anastomosis, showing complete absence of inflammation.

colon anastomosis, the only such incident in this series.

Three patients died 12 to 30 months postoperatively with recurrence of carcinoma. Postmortem examination in these three cases showed no evidence of esophagitis, colitis in the segment of transplanted large bowel, or duodenitis (Fig. 1).

Those patients who were discharged from the hospital, nine in number, had normal appetites, with ingestion of food in normal quantities. All but one of these patients showed an improved nutritional status. Weight gain averaged from 5 to 40 lb. Hemoglobin, hematocrit, and serum proteins were normal in all patients after recovery from the operation, as shown in the accompanying Table.

The commonest nonfatal postoperative complication was diarrhea. This occurred in five of the nine surviving patients and was associated with eating. This persisted from two to three months.

Delay in emptying of the colon transplant occurred in three patients in whom the splenic end of the colon was used for the proximal anastomosis. All of these patients complained of nocturnal regurgitation. Re-

*Results of Replacement of the Lower Esophagus and Stomach with Transverse Colon—Mortality*

| Lesion, Location | Deaths | | | | Living | |
|---|---|---|---|---|---|---|
| | No. | Immediate Post-operative | Late | Average Survival Time, Mo. | Alive | Survival Time, Mo. |
| Carcinoma of esophagus with involvement of stomach | 5 | 1 | 2 | 18 | 2 | 6-12 |
| Carcinoma of stomach | 7 | 2 | 1 | 24 | 4 | 12-72 |

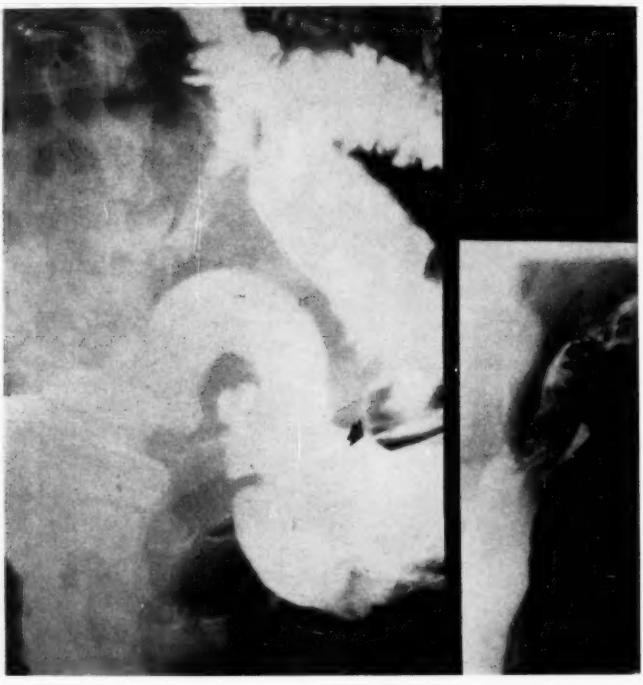

Fig. 2.—Esophagogastrectomy for carcinoma of the lower esophagus and stomach with a colon transplant between the esophagus and the distal stomach.

verse peristalsis could be demonstrated in these segments fluoroscopically but gave no further symptoms.

## Report of Cases

To illustrate the course of these patients, three typical cases are presented.

CASE 1 (Fig. 2).—*Carcinoma of the distal end of the esophagus with invasion of the stomach.*

A 49-year-old Negro man was admitted to Cleveland City Hospital on May 20, 1956, complaining of dysphagia of one year's duration. Esophagrams demonstrated an irregularity of the distal third of the esophagus with almost complete obstruction at this level. On esophagoscopy, tissue from a squamous-cell carcinoma was taken for biopsy 40 cm. from the incisor teeth. After establishment of a satisfactory chemical and nutritional balance and the usual bowel preparation, the patient was operated upon June 11. The lower esophagus and proximal two-thirds of the stomach were removed, using two separate operating teams. A segment of transverse colon was interpolated in an isoperistaltic manner between the esophagus and the distal portion of the stomach. A pyloromyotomy and tube gastrectomy were done.

Pathological sections demonstrated an extensive squamous-cell carcinoma of the lower end of the esophagus with invasion of the proximal portion of the stomach. The esophagus had been divided through normal tissue 2 cm. proximal to the lesion and the stomach divided 7 cm. distal to the lesion. The lymph nodes were negative for neoplasm.

The patient was discharged on the 35th postoperative day. After leaving the hospital, he gained 45 lb. and went back to work as a laborer in the steel mill. His appetite was normal, and he had no abdominal distress and no regurgitation. Hemoglobin, hematocrit, and serum proteins were within normal limits.

He was readmitted to the hospital on Sept. 10, 1957, complaining of severe pain in the lower chest and difficulty in breathing. A subsequent autopsy demonstrated a large secondary hepatic carcinoma, which had ruptured through the diaphragm into the pericardium. The immediate cause of death was bile pericarditis. There was no evidence of esophagitis, colitis, or gastritis.

CASE 2.—*Carcinoma of the cardia.*

A 54-year-old white man was admitted to the hospital on April 2, 1954, complaining of foul gaseous eructations and tarry stools of one month's duration. X-ray examination of the stomach disclosed a large lesion in the cardia. All bowel work was within normal limits.

He was operated upon April 5, 1954. Through a left transthoracic, transdiaphragmatic incision, the

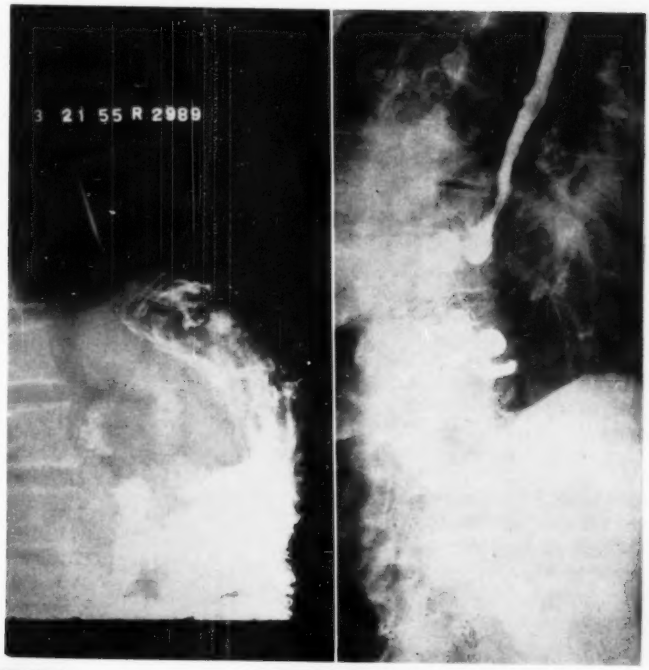


Fig. 3.—Esophagogastrectomy for a polypoid carcinoma of the cardia with a colon transplant.

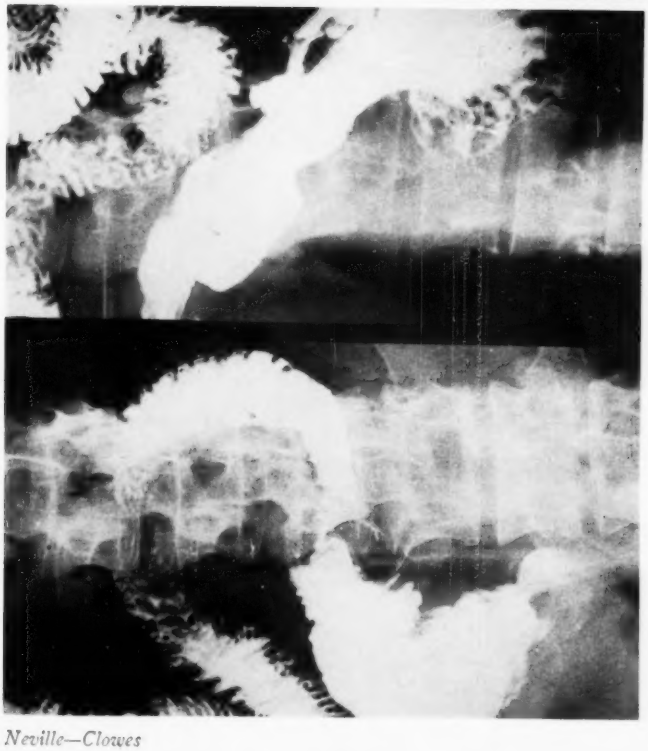

Fig. 4.—Total gastrectomy with a colon transplant between the esophagus and the duodenum.

lower 2 cm. of the esophagus, the spleen, and the major portion of the stomach were removed. A segment of transverse colon was interpolated in an antiperistaltic manner between the esophagus and the antrum (Fig. 3). The operating time was five and one-half hours.

Pathological examination showed a large, well-differentiated polypoid adenocarcinoma of the stomach. The lymph nodes removed with the specimen were negative.

His postoperative course was entirely uneventful. He was discharged from the hospital on his 15th postoperative day, at which time he was eating normally.

His subsequent course has been very gratifying. He works regularly in the steel mill, ingests normal quantities of food, and maintains his weight. His only complaint is occasional nocturnal regurgitation.

A recent blood survey showed a hemoglobin of 12.5 gm., a RBC count of 4,550,000, and a total protein of 5.8 gm. %, with an albumin of 3 gm. % and a globulin of 2.8 gm. %.

There is complete absence of esophagitis on esophagoscopy, although reverse peristalsis can be demonstrated fluoroscopically in the colonic segment.

CASE 3 (Fig. 4).—*Carcinoma of the body of the stomach.*

A 55-year-old white man entered Polyclinic Hospital on Oct. 20, 1955, complaining of epigastric pain and anorexia. X-ray examination of the stomach disclosed a large gastric ulcer on the greater curvature.

At operation on Oct. 25, when the stomach was cut across during a subtotal resection, it appeared that there was carcinoma at the line of transsection. For this reason the abdominal incision was continued into the chest; the diaphragm was divided to the hiatus, and the remainder of the stomach and lower esophagus were removed. A segment of transverse colon was interposed in an antiperistaltic manner between the esophagus and the duodenum.

His postoperative course was entirely uneventful, and he was discharged on the 12th day, eating normally.

Subsequently he gained weight, although he never did regain all of the weight lost during his illness. However, he had a normal appetite and was able to eat three full meals daily. He returned to work and was active as a captain of a bowling team.

He was readmitted to the hospital on July 7, 1957, with evidence of large-bowel obstruction. Exploratory laparotomy demonstrated extensive carcinomatosis.

Fig. 5.—Microscopic examination at the level of the esophagocolon anastomosis in a patient dying of carcinomatosis 24 months following total gastrectomy. Note complete absence of esophagitis and colitis.

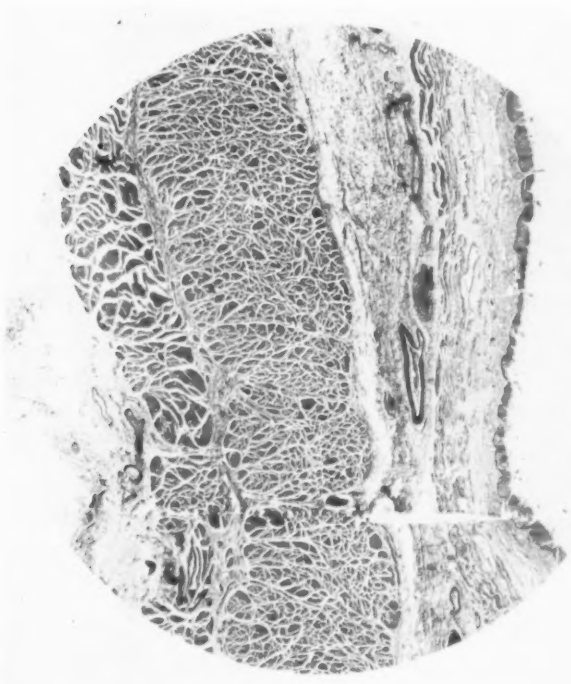

Fig. 6.—Microscopic examination of the esophagus 1 cm. above the esophagocolon anastomosis 18 months after a colon transplant.

Postmortem examination of the lower esophagus, transplanted colon, and duodenum showed complete absence of inflammation in all three segments, both grossly and microscopically (Figs. 5 and 6).

## Comment

Unfavorable results following total gastrectomy by the usual techniques led us to investigate methods of creating a pouch reservoir between the esophagus and the duodenum.

Since the first total gastrectomy by Schlatter in 1897, esophagojejunostomy, either in the form of a jejunal loop, with or without an accompanying enteroenterostomy, or a Roux en-Y type of anastomosis, has become the most accepted procedure. Anatomically the jejunum is ideally situated to establish esophagointestinal continuity, and physiologically these procedures have certain disadvantages.

In a critical analysis of 63 total gastrectomies, Scott and Longmire [14] found that very few patients gained weight equal to the weight lost prior to operation. Many of their patients had nutritional difficulties because of inability to eat satisfactorily. The food capacity of all the patients was limited, and epigastric fullness after meals was a common complaint. In many, because of the severity of the dumping syndrome, the oral intake is self-limited, thereby contributing further to their inadequate nutrition. Distressing symptoms from esophagitis due to regurgitation of alkaline jejunal contents have been manifest when a loop of jejunum has been used. Although a Roux en-Y type of esophagojejunostomy has rectified the latter, in neither of these methods is a pouch reservoir present to prevent the bolus of food from passing rapidly into the midjejunum. Also, when the duodenum is completely bypassed, nitrogen and fat absorption are significantly curtailed, as measured by their increased fecal excretion.[2,10,16] For this reason esophagoduodenostomy has been advocated.[2] Here again, there is not a

reservoir to permit the slow passage of food into the duodenum, and the dumping syndrome is prevalent.

For these reasons, in the past few years, several groups have been interested in interposing a viable segment of bowel between the esophagus and the duodenum. This creates a pouch in which the bolus of food can pass intermittently into the duodenum. Theoretically digestion should be improved and nutrition more adequately maintained.

The jejunum has been used both as a single tube connecting the esophagus with the duodenum [4,10] and as a loop with an enteroenterostomy.[7] The results have been favorable. Complications have been minimal, the mortality low, and the undesirable postoperative symptoms lessened.

Colonic segments, varying from the right ileocolon to the transverse colon, have been used successfully to create a gastric reservoir.[12] On this continent Hunnicutt [5,6] was the first to use a portion of the ileocolon as a gastric substitute. At the same time, Lee had experimental success with this same procedure in the dog.[8] Since then, State, Barclay, and Kelly [15] and Watkins [17] have reported favorably on the use of the transverse colon to replace the stomach. The latter not only has used this segment of bowel in reconstructions following total gastrectomy but has interpolated it between the upper gastric remnant and the duodenum after resections for benign disease. Moroney, in England, has likewise utilized this procedure.[11]

Although our original interest in the colon was its use as an esophageal replacement, the satisfactory results obtained in these cases led us to investigate its use as a gastric substitute (Fig. 7).

In order adequately to replace the stomach, the substitute must meet certain criteria. Anatomically it is easy to mobilize. It has to be resistant both to acid peptic digestion and to the alkaline duodenal contents. Furthermore, it should prevent esophagitis and be contractible enough to

Fig. 7.—Photograph of a colon transplant immediately following total gastrectomy. Arrows point to proximal and distal suture lines.

propel the bolus into the duodenum. Also, the unfavorable postoperative sequelae manifested in complete duodenal bypass should be remedied.

There is no question that the transverse colon anatomically lends itself to serve as a replacement for the stomach even more than does the jejunum. Furthermore, because of its rich vascularity, one need not worry about compromising its blood supply if the middle colic artery and vein are left intact.

Postoperative esophagoscopy has disclosed no esophagitis. Absence of esophagitis, colitis, or duodenitis by gross and microscopic examination at autopsy of patients who died after two or three years of progression of their disease suggests that the colonic mucosa is resistant both to acid and to alkaline digestion.

That all patients had fairly normal appetites and showed improvement in their nutritional status, as measured by hemoglobin, total protein, and strength, would suggest that this substitute gastric reservoir does have certain inherent advantages.

Time and accumulated data only will tell whether or not the procedure is worth the effort in the patient who may die within a few months of his carcinoma. From our favorable results and those reported by Watkins and Hunnicutt, at the moment it appears that the procedure is worth while in selected cases. If the original lesion has not spread beyond its local confines, the patient may live long enough to derive the additional benefits for which the operation is designed and which it appears to offer.

## Summary

1. The technique of interposing the transverse colon between the esophagus and the duodenum to serve as a gastric reservoir is outlined.

2. The results and complications in 12 patients operated upon for malignant disease are discussed.

3. The advantages of using this portion of the bowel as a substitute stomach are presented.

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## DISCUSSION

DR. JAMES S. BATTERSBY, Indianapolis: We, too, have become interested in the use of the colon for reconstruction of the upper gastrointestinal tract. In 1952 we began our study of this particular problem. The approach was somewhat similar to that taken by Drs. Neville and Clowes. We have explored the possibility of using this tube to reconstruct the upper gastrointestinal tract primarily for esophageal lesions. However, it has been extended to include the stomach.

The route by which the colon can be used depends entirely upon the height to which one has to go in replacing the esophagus. We have explored these routes: the antethoracic route, should one have to go an exceedingly long distance in the neck to get above the lesion in the gastrointestinal tract; the intrathoracic route, and the mediastinal route.

This procedure has been used in a total of 27 cases, 7 of them having been benign lesions of the upper gastrointestinal tract primarily bridging a defect of the esophagus. Operations for atresia of the esophagus totaled 5, and 15 were for carcinomas.

The complications we have encountered in this particular problem were roughly these: Ten per cent of our patients have had inadequate blood supply in the collateral circulation of the colon to support a sufficient length of bowel. An anastomotic leak has occurred twice in atresia patients with the anastomosis to the cervical part of the esophagus. When we have done an intrathoracic bypass procedure, leaving the esophagus in place, no leak or empyema has occurred. We have had thrombosis of a collateral vessel once. Peptic ulceration has occurred at the cologastric anastomosis on two occasions, in one of which it perforated into the free peritoneal cavity.

The mortality for the group of 27 patients was 3. In our experience, the use of the colon for either bypass or interpolation as a substitute for the stomach or esophagus has had a lower rate of complications and mortality than that of any other of the structures employed, such as jejunum and plastic prosthesis.

DR. CLAUDE J. HUNT, Kansas City, Mo.: I have been very much interested in this paper concerning replacement of the stomach by a segment of the colon, right or transverse. Many attempts have been made to improve the standard procedure of esophagojejunostomy with enteroenteroanastomosis. Because the results with that type of procedure have not been good, often because of reflux esophagitis, malnutrition, and failure of the patient to gain weight, the patient was often in about as bad condition after the operation as he was before.

We have made no attempt to replace the stomach by a segment of the right colon or transverse colon, but we have replaced the stomach by a double parallel loop of jejunum. In 13 cases, presented several years ago before the Western Surgical Association in which the pouch operation, accompanied by a Roux en-Y procedure, was performed, the results have been encouraging. A food pouch, comparable to the remaining stomach after a subtotal gastrectomy, is formed out of the jejunum, and the Roux en-Y diverts the duodenal contents and prevents reflux esophagitis.

(Slide) You will note that in this replacement procedure we have taken a segment of the jejunum and brought it up either anterior to the colon or through the mesentery of the colon, and we have doubled the loop around so that one loop is antiperistaltic and one loop is peristaltic. An anastomosis is made between the two parallel segments of the jejunum. We have used this double loop of jejunum for the purpose of making a larger food basket. Others have used one segment of the jejunum interposed between the esophagus and the duodenum. This does not provide an adequate food receptacle. We have used two segments, doubling it around as shown, which makes a nice, large pouch. This makes a large food container, and these patients can eat a full meal.

(Slide) This slide shows that in the formation of the pouch we have divided the jejunum below the ligament of Treitz and have brought the distal end of the jejunum up either anterior or posterior to the colon, as it seems best. A short distance from the distal end of the divided jejunum we have anastomosed it to the esophagus, leaving a variable length of the jejunum to bring down parallel to the ascending limb for the pouch.

We have done a Roux en-Y anastomosis, which I think is an important thing in all total gastrectomies if one is going to anastomose the esophagus to the jejunum, for with a Roux en-Y anastomosis there is very little or no reflux of duodenum contents and no subsequent esophagitis.

When one has anastomosed the esophagus to the jejunum, and has performed a Roux en-Y anastomosis, if the patient is not in a satisfactory condition, so that the procedure of the pouch formation can be continued, the segment distal to the esophagus can be divided near the anastomosed esophagus and the end of the jejunum closed. Usually, however, the patient is in satisfactory condition, and the end can be brought parallel to the ascending limb and an enteroenteroanastomosis done, making a pouch.

(Slide) This slide shows the pouch after it is completed. It is adequate for food intake. These patients can eat quite a satisfactory meal. In

every instance in which we have done this operation, the patient has gained a reasonable amount of weight. We pass a nasal tube through the stoma, past the Roux en-Y. We use this as a device for the Murphy drip method for feeding the patient for a few days.

(Slide) This slide shows the manner in which the pouch empties itself. The barium meal is shown in the pouch emptying out slowly and gradually, not dumping itself into the jejunum, but emptying in a regular rhythmic manner.

(Slide) This shows the procedure on one slide, demonstrating how the distal limb of the jejunum is brought up and anastomosed to the esophagus, the short, protruding segment being brought down to form the resulting pouch.

Of 13 of these patients, 1 lived 23 months after operation. Several have lived 15 months. The next longest survival was 19 months. There were 3 deaths in the 13 cases. In one there was an en masse removal of the stomach and a portion of the transverse colon, with a reconstruction of the colon by end-to-end anastomosis. There developed such an enormous amount of distention in the proximal colon and the cecum that it was feared a leak at the suture line would develop; so a cecostomy was done. At autopsy a leak was found to have occurred at the colon reconstruction anastomosis as a result of intracolonic pressure. Cecal decompression was too long deferred.

The two other patients died of leaks at the esophagojejunum union. This slide shows the postmortem specimen of a patient who died 23 months after total gastrectomy. There is no ulcer at the site of the anastomosis between the esophagus and the jejunum, no evidence of esophagitis, and no stricture or contraction. These patients have no difficulty in swallowing and no dysphagia.

(Slide) This slide shows nine cases. The results have been satisfactory. Four have since been added. In most instances the procedure is a palliative one and is usually not an operation in which cure is expected.

We have carried out exploration in these patients through a high midline incision. In two instances a sternal splitting or costal-cartilage division was done; in one instance we did a thoracoabdominal exploration for a lesion that extended up above the hiatus to the lower esophagus.

DR. WILLIAM E. NEVILLE, Cleveland: I wish to thank the discussants for their very informative remarks, especially Dr. Battersby, whom we all know as one of the pioneers in this country in the use of the colon as an esophageal substitute. It was due to his original enthusiasm for the procedure that we embarked on such a program, in 1954.

With regard to the esophagus alone, we have done 34 colon transplants for the esophagus. We are satisfied with our results. The one point Dr. Battersby made is that one should create a pouch reservoir between the esophagus and the duodenum. That is the essence of the operation.

Dr. Hunt has accomplished the same result using the jejunum. Personally, I don't think it makes any difference which segment of bowel one uses. The colon has a much larger capacity. Also, the transverse colon is right in the operating field following a total gastrectomy. All one has to do is to select an appropriate length and divide the bowel proximal and distal to the middle colic vessels. In our hands at least, for the reason enumerated, the colon does offer some advantages.

# Response to Transfusion as Guide in Management of Upper Gastrointestinal Hemorrhage

DANIEL W. ELLIOTT, M.D.; RICHARD HARTLE, B.S.; FOSTER MARSHALL, M.D., and ROBERT M. ZOLLINGER, M.D., Columbus, Ohio

Three things remain paramount in successful management of massive upper gastrointestinal hemorrhage. These are knowledge of the source, accurate estimation of the rate of blood loss, and adequate replacement. In addition, prompt surgical intervention will be required for some patients lest exsanguination occur. With whole blood readily available, and with close cooperation between physician and surgeon, as the current literature so often admonishes, convincing evidence of effective management should appear in a lowered mortality rate for all bleeding patients, whether operated upon or not. A survey of the past 10 years' experience has been made to evaluate the effectiveness of this approach.

During this period, management has included certain important steps. When a patient bleeding heavily from the upper gastrointestinal tract is encountered, 6 pt. (3000 cc.) of whole blood is crossmatched, and initial therapy for shock is given as needed. An estimate of initial blood loss is made, and prompt replacement is begun. It is extremely important that, as each pint of blood is administered, a pint is added to the reserve, so that 6 pt. is always available in the event of emergency, or need for surgery.[1]

Time is then taken to diagnose the source of hemorrhage, or at least to place it in one of three principal categories for purposes of management. These are (1) esophageal varices; (2) blood dyscrasias with coagulation defects, such as hemophilia and leukemia, and (3) all other lesions of the upper gastrointestinal tract, at or below the diaphragm. Usually this can be done at the completion of the history taking, physical examination, and a few preliminary laboratory procedures, which include determinations of prothrombin time, venous clotting time, platelet estimation, and sulfobromophthalein (BSP) retention if cirrhosis is suspected.[2]

A tube is passed into the stomach routinely if there is no enlargement of the spleen or liver or other stigmata of varices. This is done in all cases because, if the patient has been vomiting, the stomach should be emptied and placed at rest. If there has been no vomiting, it will be very useful to know, in later management, whether the stomach contained blood while there was active bleeding.

If the source of bleeding is unknown, x-ray examination is performed as soon as possible after the blood pressure is stable and the stomach aspirated. For this, whole blood must be available, and a clinician should accompany the patient to the x-ray department to facilitate its prompt administration when necessary. No restriction is placed on fluoroscopy, since the best possible examination is needed. Emergency x-ray examination has proved most useful, since it has accurately localized the lesion in 75% of instances. This rate of accuracy is comparable to that obtained in elective x-ray examination later, after all bleeding has ceased.

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From the Department of Surgery and the Medical Center of The Ohio State University College of Medicine.

TABLE 1.—*All Admissions for Upper Gastrointestinal Hemorrhage in Ten Years, 1948-1957*

| | Cases | Per Cent |
|---|---|---|
| Esophageal varices | 85 | 12.9 |
| Blood dyscrasias with coagulation defects | 44 | 6.7 |
| All other causes for bleeding | 529 | 80.4 |
| Totals | 658 * | 100 |

* A total of 658 separate admissions and bleeding episodes in 602 patients.

TABLE 2.—*Clinical Types of Hemorrhage: All Lesions Except Varices and Blood Dyscrasias*

| | Cases | Per Cent |
|---|---|---|
| Mild | 150 | 28.7 |
| Chronic | 92 | 17.7 |
| Massive-acute | 279 | 53.6 |
| Totals | 521 * | 100 |

* This table excludes eight cases with gastrointestinal hemorrhage as terminal event in known disseminated cancer.

Table 1 presents the distribution of all patients with upper gastrointestinal hemorrhage, by category of lesion encountered, observed at the University Hospital in the 10-year period of 1948 through 1957. The first two categories, varices and blood dyscrasias, each present intricate and difficult considerations in surgical management peculiar to themselves, and cannot properly be considered with the third. Therefore, patients with either varices or blood dyscrasias have been excluded from the remainder of this study. Perhaps a higher proportion of blood dyscrasias than is usually encountered appears here because of the specific interests of the department of medicine in that group of diseases. However, 80% of all upper gastrointestinal bleeding problems fall into the third group, for which surgical intervention can offer definitive therapy. This group includes not only peptic ulcer but also benign and malignant tumors, gastritis, and hiatus hernia with hemorrhage, as well as those cases in which no definitive diagnosis could be established. These conditions are all included here because they must be considered in managing patients who are acutely bleeding from the upper gastrointestinal tract. Two-thirds of this third group had peptic ulcer, as expected.[3]

The estimated rate of blood loss, as emphasized by others,[4] has been the guiding consideration in subsequent management of patients with these lesions amenable to definitive surgery. When the rate of blood loss is mild or chronic, the results of transfusion therapy alone are good. It is in patients with "massive" blood loss which may require surgical intervention that real problems in treatment occur. The reported mortality rates in treatment of such blood loss depend on the precise definition of "massive."[5,6] Here, one or more of three criteria were accepted as being indicative of a massive hemorrhage: (1) clinical shock, with blood pressure falling below 90 systolic; (2) the requirement of 3 pt. (1500 cc.) of blood or more in any one 24-hour period to maintain a stable blood pressure, and (3) the hemoglobin level falling acutely below 9.0 gm. %. In addition, there must have been an acute episode of bleeding within six days of hospitalization, or the beginning of therapy.

From these criteria all patients with upper gastrointestinal hemorrhage from any lesion, exclusive of varices or blood dyscrasias, have been divided into three groups: (1) mild bleeding, insufficient to meet criteria for massive hemorrhage; (2) chronic bleeding, of longer duration than

TABLE 3.—*Criteria for Massive Acute Upper Gastrointestinal Hemorrhage with Distribution of Cases Attributed to Each*

| | Cases | Per Cent |
|---|---|---|
| Clinical shock | 105 | 38 |
| Required 3 pt. blood or more per 24 hours | 116 | 42 |
| Hemoglobin below 9 gm. % | 58 | 20 |
| Totals | 279 * | 100 |

* A total of 279 separate admissions and bleeding episodes in 262 patients.

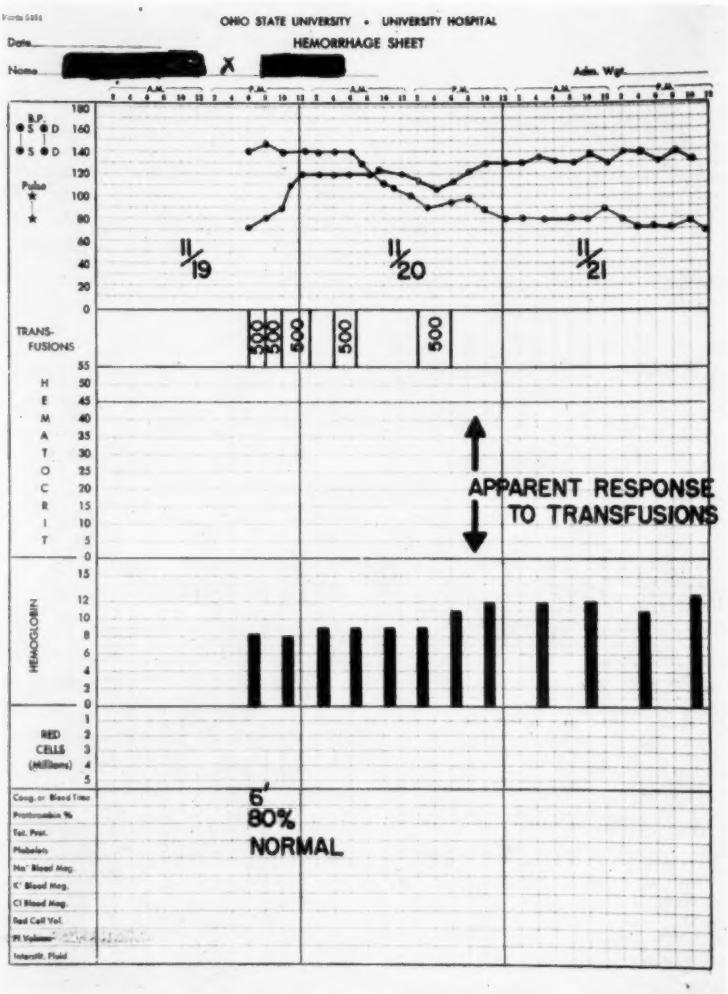



Fig. 1.—"Hemorrhage Sheet" helps in giving accurate replacement transfusions, by combining in one place the (1) pulse rate, (2) systolic blood pressure, (3) pints of blood given and time when given, and (4) hemoglobin response. The arrow points to first evidence of response to transfusion therapy.

six days, and (3) massive bleeding, by the criteria outlined above. For perspective, these groups are presented in Table 2, in which it can be seen that criteria for massive bleeding were met in only slightly more than half of the cases encountered. The number of patients attributable to each of the three criteria for massive bleeding is presented in Table 3. Shock appeared in 38%, and a requirement of 3 units of blood or more in 24 hours accounted for the inclusion of an additional 42%. The hemoglobin level was the determining criterion in only 20% of these patients, but this level of 9.0 gm. % was necessary to include all deaths encountered. The red cell count was thought unreliable and was not accepted as another criterion. Blood volume determinations were not employed sufficiently often in acute hemorrhage to enter into these criteria, al-

though they have proved valuable in the evaluation of patients with chronic blood loss.[1]

Some patients who appear to be bleeding massively will respond to adequate transfusion therapy, bed rest, and sedation, with either gastric suction or active antacid therapy. However, when an individual patient is first seen, it has been impossible to tell whether he will stop bleeding with this therapy or has already done so. Because of this, prompt operative intervention for all massively bleeding peptic ulcer patients has been undertaken elsewhere with good results.[7] However, the risk of surgery is understandably greater during the acute bleeding episode than it might be after hemorrhage is controlled. Since this may be possible, each patient bleeding massively has been given a chance to demonstrate whether he will respond adequately to transfusion therapy. However, when surgical intervention is withheld for a period of observation, an obligation is assumed to reevaluate the adequacy of transfusion and the need for operation at frequent intervals. This must be done every four hours at first, and later every eight hours, till an adequate sustained response to transfusion has been clearly demonstrated.

An efficient and comprehensive evaluation, at such frequent intervals, has been possible with the aid of a specially prepared, printed "hemorrhage sheet" (Fig. 1). This is placed on the front of the patient's chart and gathers together in one convenient place the essential data needed to evaluate the patient's course: (1) the blood pressure and pulse rate, (2) blood administered, and (3) hemoglobin response. The need for leafing through the chart repeatedly to put together these data is eliminated. The principle of such a form is nothing new to experienced clinicians. However, there is a special advantage in having this form printed and distributed in advance to all nursing stations throughout the hospital, since it is then used on all services. When the patient's response to blood is graphically apparent on such a sheet, more nearly accurate replacement transfusion therapy is given.

During the past 10 years, the increasing availability of whole blood, together with an appreciation of the dangers of hemorrhagic shock, should have made a period of delay for evaluation safer and the over-all mortality lower. An important goal of this study has been to determine whether the period for response to transfusion is worth while, and, particularly, to define its limitations.

## Results of Transfusion Therapy in Massive Acute Hemorrhage

Treatment has been evaluated only in those patients with massive acute hemorrhage, since these present the real problems in surgical management. In the 150 patients with mild bleeding there were no deaths; among the 92 with chronic blood loss, 3 deaths were apparently not related to the bleeding episode.

Of the 279 patients having massive hemorrhage from any upper gastrointestinal lesion except varices or blood dyscrasias, 206 or 74%, initially responded to supportive and transfusion therapy. To be considered as having shown a satisfactory response, external signs of bleeding must have disappeared and vital signs become stable, and, if blood is still being given, an appropriate rise in hemoglobin level must have followed. Such a satisfactory response is illustrated on the hemorrhage sheet in Figure 1. It must have persisted for 24 hours or longer to be called a response. If, after 24 hours of stability, subsequent signs of hemorrhage appeared, "rebleeding" was said to have occurred. The 72 patients who never achieved any such period of satisfactory response to transfusion either had emergency surgery performed or bled till death ensued.

Which patients will not respond to transfusion therapy? If signs could be found that would clearly identify this one-fourth of all cases, earlier operation could be per-

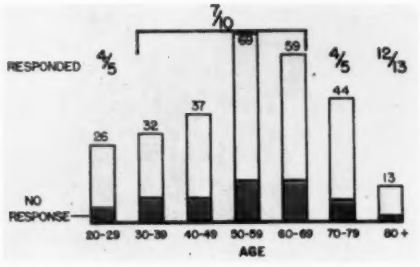



Fig. 2.—Age *vs.* response to transfusion. The number of patients in each decade of life is shown. The upper light part of each bar indicates the number responding to transfusion. There is no substantial difference in per cent responding among the decades except that the youngest and the oldest (70 and older) showed a better incidence of response.

formed, with a lowered mortality. Many of the indications now accepted for emergency surgical intervention set forth some combination of factors which may herald failure of transfusion therapy.[5,9]

The age of the bleeding patient has often been a matter of crucial concern in guiding surgical management, since it is widely believed that in older patients, with arteriosclerotic arteries, bleeding is less likely to stop without operation.[5,10] In addition, the risks of hemorrhagic shock, as well as of operation, rise with increasing age.[11] However, in this study, illustrated in Figure 2, no appreciable difference in the incidences of satisfactory response to transfusion appeared among the various decades of life, except that both the older (above 70 years) and the youngest age groups (below 30 years) showed a slightly better incidence of favorable response. Particularly in patients over 70, where complicating diseases often increase operative risks, there appears to be a distinct advantage in attempting to obtain control of hemorrhage with supportive and transfusion therapy. It appears that advanced age should not be considered among the indications for surgical intervention in massive upper gastrointestinal hemorrhage.

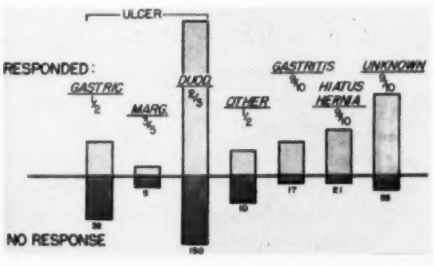
Some symptoms which are commonly supposed to suggest bleeding so massive that it will not respond to transfusion therapy are presented in Table 4. All patients had melena, and hematemesis occurred in two-thirds. However, as many patients responded to transfusion after hematemesis as responded in the whole group. Clinical shock proved to be a graver prognostic sign. Only about one-half of patients bleeding into shock subsequently had a satisfactory response to transfusion.

The specific diagnosis of the bleeding point as finally determined by operation, autopsy, or x-ray examination yielded only a moderate indication of what could be expected from transfusion therapy. The distribution of the 279 cases among the diagnoses encountered is illustrated in Figure 3. Only slightly less than one-half of patients bleeding from a gastric ulcer responded to transfusion, whereas in bleeding from a duodenal ulcer, almost as many responded as in the average for the whole group. Only when bleeding arose from

TABLE 4.—*Significant Symptoms in 279 Admissions for Massive Acute Upper Gastrointestinal Hemorrhage and Response to Transfusion Therapy*

| | Incidence | | Responded | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Hematemesis | 188 | 67 | 136 | 72 |
| Shock | | | | |
| (Systolic below 90) | 105 | 38 | 56 | 53 |
| All cases | 279 | 100 | 206 | 74 |

Fig. 3.—Diagnosis *vs.* response to transfusion. The number of patients with each diagnosis encountered is represented by a bar. The lighter portion above the line indicates the number responding to transfusion therapy, and the proportion responding is indicated by the fractions. The "other" group includes three gastric carcinomas, three leiomyomas, and 1 each lymphosarcoma, ulcerated diverticulum, hemangioma, and duodenal erosion by metastatic cancer.



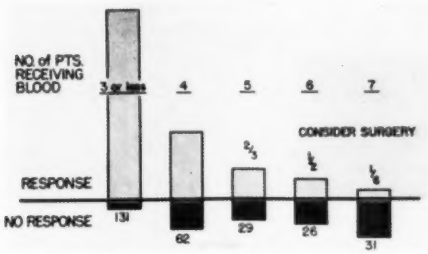



Fig. 4.—Patients are divided according to the greatest number of pints of blood received in any one 24-hour period. The number responding to transfusion therapy is represented by the lighter portion of the bar above the line. Blood administered at operation is not included here.

acute gastritis, hiatus hernia, or in the absence of demonstrable pathology could a good response to transfusion be expected, and in each of these conditions 1 in 10 patients failed to respond.

The patients bleeding massively, and yet in whom no pathology can be demonstrated by x-ray or any other means, present a particular dilemma to surgeons. It is encouraging to note that a good response to transfusion therapy was obtained in 49 of these 55 cases. This appears to substantiate a natural reluctance to intervene surgically in these cases. However, in the six patients who failed to respond and were operated upon without a lesion being found, "blind" subtotal gastrectomy achieved initially satisfactory results, as has been reported by others.[12]

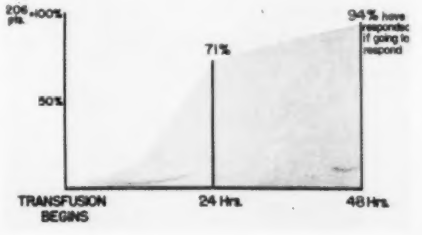
Among other factors examined and found to be of no help in predicting response to transfusion therapy were (1) a history of previous hemorrhage, (2) sex or race, (3) initial hemoglobin level, or (4) rapidity of blood loss before treatment began.

In summary, no very reliable factors for prognosis of response to transfusion therapy could be established in this study. Generally, it appears that, in this group, the patient least likely to have a favorable response would be between 50 and 70 years of age, with a gastric ulcer, and has exhibited shock. The patient most likely to obtain a good response from transfusion therapy is either below 30 or above 70, with gastritis, hiatus hernia, or no demonstrable lesion by x-ray, and has not been in shock.

To determine whether a given patient will respond favorably to transfusion therapy, it must be given a trial. What constitutes an adequate trial before emergency operation is considered? The rate at which blood must be administered to maintain stable vital signs during a trial of transfusion therapy has previously been considered to have prognostic value.[3] In Figure 4, the patients so treated are grouped according to the greatest number of pints of blood administered in any 24-hour period. Three-fourths of the patients who required 4 pt. (2000 cc.) per 24 hours responded to transfusion. Two-thirds or more of the patients who required as much as 5 pt. (2500 cc.) in a 24-hour period still responded. However, when 6 pt. are required within 24 hours the chances for a favorable response drop to less than 50%, and emergency operation appears indicated.

In retrospect, it appeared remarkable how early in the course of transfusion therapy the favorable response could be identified. Figure 5 illustrates this. When only the patients who eventually responded are considered, 71% had shown this response within 24 hours of beginning treatment. At the end of 48 hours almost all, or 94% of patients who were going to respond had done so. There is, therefore, very little to be gained in continuing a trial of transfusion therapy beyond 48 hours in the hope that a favorable response may yet be obtained.

Fig. 5.—Only patients (206) who eventually responded to transfusion therapy are represented here. Of these, 71% showed clear-cut evidence of response within the first 24 hours of treatment, and nearly all had responded within 48 hours.



The indications for surgical intervention have been determined by the two principal signs of failing transfusion therapy. These are (1) failure of response to as many as 5 pt. of blood within any 24-hour period, and (2) failure of response to any amount of blood after 48 hours of therapy. In addition, rebleeding under treatment has been considered a surgical indication, and this occurred in 39 patients, or one-fifth of those who initially responded to transfusion therapy.

Emergency operation was performed in 80 patients, or 29% of the whole group. In addition to these, 31 elective procedures were performed after hemorrhage was controlled, usually within a few days.

Altogether, 111 operations were performed for a variety of lesions, but principally peptic ulcer. These included 93 subtotal gastric resections, about equally divided between Billroth I-with-vagotomy and Billroth II procedures. The remainder included four vagotomies with gastroenterostomies, six gastrotomies without definitive resection, and seven excisions of leiomyomas, or other local excisions.

The mortality for these procedures is summarized in Table 5. These rates represent a hospital-wide experience and include approximately 43% of clinical patients operated upon by residents under supervision. The average mortality rate for emergency procedures, 16%, is higher than the approximately 13% reported when a larger proportion of patients is operated upon.[7]

TABLE 5.—*Results of Surgery in 111 Operations for Massive Acute Upper Gastrointestinal Bleeding*

| | Admissions | Deaths | Mortality |
|---|---|---|---|
| Emergency operation for uncontrolled hemorrhage | 60 | 9 | 15% |
| Emergency operation for rebleeding | 20 | 4 | 20% |
| All emergency operations | 80 | 13 | 16.25% |
| Elective operation after hemorrhage controlled | 31 | 1 | 3% |
| Totals | 111 | 14 | 12% |

TABLE 6.—*Over-All Results in 279 Admissions of 262 Patients with Massive Acute Upper Gastrointestinal Hemorrhage, 1948-1957*

| | Cases | Deaths | Mortality |
|---|---|---|---|
| Emergency operation for uncontrolled hemorrhage | 60 | 9 | 15% |
| Transfusion therapy, including operation for rebleeding or electively | 219 | 21 | 9.6% |
| Over-all results | 279 | 30 | 10.7% |

However, the group reported here included all lesions for which surgery was performed, excluding only varices and blood dyscrasias. Since all of these patients had failed in response to a trial of transfusion therapy, they represent the graver risks in the whole series. The striking difference to be noted is that when operation can be deferred till after a response to transfusion is achieved, it can then be undertaken, often within a few days, with an elective mortality rate of 3.3% or one-fifth of that for emergency surgery.

The slightly lower mortality, of 9.6%, from all causes in those patients treated primarily with transfusion therapy rather than operation appears to attest to the safety of this procedure (Table 6). However, where operative intervention for the acute bleeding episode supplements transfusion therapy, as it does here, operative mortality ought not be compared with the mortality of nonoperative treatment, and should not be reported alone. The real test of a program of therapy lies in the result it achieves in the whole group of patients observed. These results are presented in Table 6. A reasonably respectable over-all mortality experience of 10.7% appears to support the concept of treatment by transfusion therapy, followed by operation if this fails. However, in examining this experience year by year, it is disappointing to note that there is no apparent trend toward improvement in mortality, and this absence has been noted by others.[13]

How is the mortality for massive acute upper gastrointestinal hemorrhage to be im-

TABLE 7.—*Deaths Following Massive Acute Upper Gastrointestinal Hemorrhage*

| | | No. | Technical Failures or Complications | Delay or Indecision |
|---|---|---|---|---|
| Operative | | | | |
| Emergency, for uncontrolled hemorrhage, within 48 hr. | | 9 | 7 | 1 |
| Emergency, for rebleeding | | 4 | 4 | 2 |
| Elective | | 1 | 1 | 1 |
| Nonoperative | | | | |
| Responded to transfusion | | 2 | 0 | 0 |
| Too ill for operation when bleeding began | | | | |
| Gen'l peritonitis | 4 | | | |
| Acute pancreatitis | 1 | | | |
| Crushed chest | 1 | | | |
| Uremia—Coma | 1 | 7 | 0 | 0 |
| Failures of transfusion therapy * | | 7 | 0 | 6 |
| Totals | | 30* | 12 | 10 |

* In retrospect, only one patient who died received inadequate blood replacement.

proved? With the benefit of hindsight, the 30 deaths reported here were analyzed for contributing factors. The most vulnerable appears to be delay or indecision about operative intervention. This analysis is presented in Table 7. Although technical failures and complications must be implicated in 12 of the postoperative deaths, delay may have contributed to 4 of these.

There were no deaths due to unnecessary surgery. In only one death, probably too little blood was given. However, delay in undertaking surgery could be identified in 10 deaths, or one-third of the total mortality. It appears that while the ready availability of whole blood makes a trial of transfusion therapy easier and safer, it also may contribute to a temptation to postpone decision about operation. This may be one of the factors keeping the mortality rate high.

## Summary

A policy of treatment for massive acute upper gastrointestinal hemorrhage is evaluated which delays emergency operation while vigorous transfusion therapy is given, in the hope that this will control the hemorrhage. Altogether, 279 bleeding episodes in 262 patients, observed in a 10-year period, have been studied, with hemorrhage from all sources except esophageal varices and blood dyscrasias. Criteria for the severity of hemorrhage have been designed to include those cases usually considered for emergency operative intervention.

Three-quarters of these patients responded to vigorous transfusion therapy, with a mortality from all causes of 9.6%. Over-all mortality for the series was 10.7%.

No reliable prognostic signs for determining which patients would respond could be found. Contrary to previous reports, age had little influence on response to transfusion. Generally, those patients above 70 and below 30 responded more frequently than did the average of the group.

If shock occurred, only one-half of the patients responded. Gastric ulcers responded in less than one-half the patients; duodenal ulcers, in two-thirds, while 9 out of 10 patients with gastritis, hiatus hernia, or no demonstrable lesion responded favorably.

A specially printed graphic "Hemorrhage Sheet," in use throughout the hospital, helped ensure accurate blood replacement.

Failure of the trial of transfusion therapy and clear-cut indication for emergency operation was manifested by (1) a need for more than 5 pt. (2500 cc.) of blood in any single 24-hour period and (2) absence of definite response after 48 hours of treatment. Of all patients who eventually responded to transfusion therapy, 94% did so within 48 hours.

Of all patients who responded, one in five had rebleeding under therapy. This is also an indication for emergency surgery.

A retrospective analysis of mortality shows no trend toward improvement. Probably adequate blood replacement was given in all cases of death but one. However, a factor of indecision about operative intervention contributed to one-third of the 30 deaths.

## Conclusions

Patients with massive acute upper gastrointestinal hemorrhage can be effectively managed with an initial trial of vigorous

transfusion therapy, providing its limitations are strictly observed. These are (1) failure of response to 5 pt. of blood within any 24-hour period; (2) failure of response to any amount within 48 hours, or (3) rebleeding under treatment. Any one of these indicates need for prompt surgical intervention.

A relatively fixed mortality rate has been observed over the years for massive acute upper gastrointestinal hemorrhage, despite the increasing availability and use of whole blood. New measures for these patients are needed if mortality is to be lowered. Some help may come from earlier decision about operation, guided in each patient by his response to transfusion therapy.

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## DISCUSSION

DR. STANLEY O. HOERR, Cleveland: Our approach to the problem presented by the patient who is having a severe hemorrhage from the upper gastrointestinal tract has been essentially the same as that of Dr. Elliott and his co-workers. It is particularly gratifying, therefore, to have him emphasize the things that we think are important also, namely, that the rate of hemorrhage is the decisive factor as to whether an operation is to be performed.

Our experience has been the same as Dr. Elliott's that elderly patients respond to transfusion equally as well as younger patients and that we should cease to think in terms of age as the basis for urging an emergency operation.

There can be little question that the 12 patients in the group over 80 years of age, which Dr. Elliott showed on the screen, did better on conservative measures than they would have if all of them had had emergency operations.

The criterion that we have employed for emergency or urgent operations has been a failure to respond to initial transfusions—that is, if a patient receives 3 or 4 pt. (1500 or 2000 cc.) of blood and if his circulation is not stabilized at the end of that time, in the course of five or six hours, we regard him as a candidate for emergency operation.

We also have used the 3-pt.-a-day rule. If the patient seems to require more blood than 3 pt. a day, we think an operation is in order; and if there is evidence of renewed bleeding after apparent stabilization, we think an emergency operation should be carried out. Usually, if these patients are not stabilized at once, or if they start bleeding again, there is no question about the need for operation. With the middle group, where one does not know whether the patients are going to stop bleeding, I think the "hemorrhage sheet" is going to be a great addition to our thinking.

I am going to get a copy of that sheet and take it back and employ it with our bleeding cases.

It is important to see a simple thing like a hemoglobin value show up so graphically as a guide to treatment, rather than the so-called complicated things that some of us older men have distrusted, or have never been able to learn to use correctly, such as blood volumes.

DR. DANIEL W. ELLIOTT, Columbus, Ohio: Thank you, Dr. Hoerr. We have found the hemorrhage sheet most useful. It obviates leafing through charts and searching for data, and it has encouraged the use of adequate transfusions on other services through the hospital, as well as on our own general surgery service.

# A Method for Estimating the Proportion of Stomach Removed in Partial Gastrectomy

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Those interested in the surgical treatment of duodenal ulcer by gastric resection agree that the amount of stomach that is removed at operation bears a relationship to the incidence of recurrent ulcer. It is frequently stated that at least three-quarters of the stomach should be removed if the rate of recurrent ulceration is to be kept at an acceptably low level. If vagotomy is combined with gastric resection, it appears that less of the stomach need be removed to accomplish the same results. Many different methods have been employed by surgeons to determine the percentage of stomach removed, ranging from gross estimates or a guess to calculations based primarily on weight, linear measurements, or other single variables. It appeared that a more accurate method of determining the proportion of stomach removed at the time of partial gastrectomy might be helpful. The present study was undertaken with the purpose of developing such a method.

## Material and Observations

Fifty normal intact human stomachs obtained at necropsy in the first few hours after death were carefully stripped of their mesenteric and omental fat and then weighed and measured. One hundred fifty simulated gastric resections were then carried out, and the resected pieces were similarly weighed and measured. Each stomach was cut along the greater curvature, exactly along the attachment of the gastrocolic ligament, and the following data were recorded for each entire stomach and its resected portions: weight, surface area, volume of tissue, length of lesser curvature, length of greater curvature, distance from pylorus to incisura angularis, thickness of the muscularis, and linear measurements designated *B*, *C*, *D*, *E*, *F*, and *F'*. Four thousand measurements were made on these specimens (Fig. 1).

With the entire stomach and the resected pieces thereof it was possible to calculate the proportion of the stomach removed, by weight, surface area, and volume of tissue. With a known "percentage of resection" based on these three measurements, graphs were plotted using various linear functions of the resected pieces as the abscissas and percentages of resection as the ordinates. An effort was made to determine whether there were any measurements or combination of measurements taken on the resected piece from which the percentage of stomach that was removed could be estimated. After the construction of many graphs, it was finally found possible to calculate the "percentage of resection" by correlating weight with a measurement made on the resected portion. The final formula embodied a relationship existing between the weight of the specimen and the thickness of the muscularis at the upper cut edge of the specimen. The average deviation of the percentage of

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Former Fellow in Surgery, Mayo Foundation (Dr. Heinrich). Section of Surgical Pathology (Dr. Dockerty); Section of Surgery (Dr. Priestley); Section of Biometry and Medical Statistics (Mr. Gage), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Fig. 1.—Diagram showing subdivision of stomach for purposes of estimating proportion removed at resection.

stomach resected as calculated from these figures from the actual percentage resected was found to be approximately 6% (Fig. 2).

A formula was now available (weight correlated with the thickness of the muscularis at the upper edge of the line of resection) by which to calculate percentage of stomach removed in the postmortem specimen. It was thought that this could be applied to surgical specimens as well. It seemed unlikely that the accuracy of this formula could actually be proved in surgical specimens, but efforts were made to determine whether there were any gross errors in the method.

Fourteen surgical specimens were obtained and compared with fourteen similar specimens obtained at necropsy. There were several major differences in the two groups of specimens: (1) The surgical specimen weighed more; (2) it had a thicker wall; (3) it contained more fat on the greater and lesser curvatures; (4) it appeared more engorged with blood and more edematous, and (5) it was not embalmed (Fig. 3). Since the weight of the specimen and the thickness of the wall were included in the formula, it was felt that variations 1 and 2 would not materially affect the accuracy of the formula used. Since all the fat had been removed from the specimen before

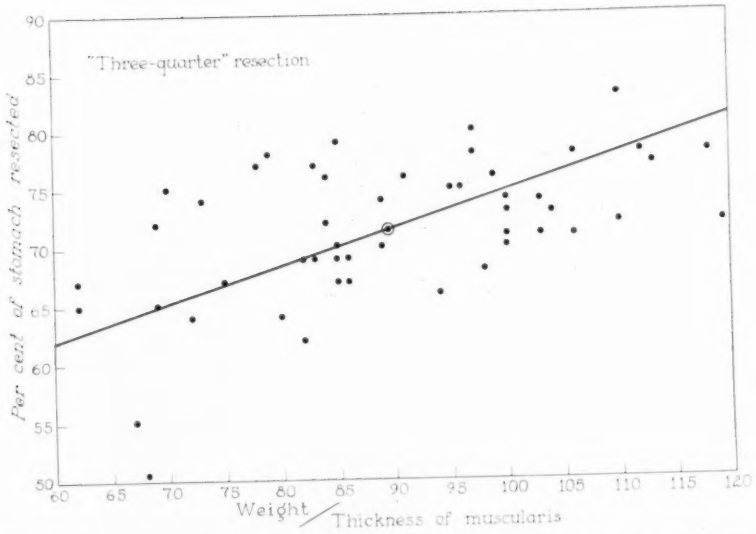


Fig. 2.—Scattergram showing calculated percentage removal by formula. Actual proportion is indicated by dots.

Fig. 3.—Before measurements are made on resected portion of stomach, fat is carefully removed from both curvatures.

weighing and measuring, the third variation was eliminated. An experiment was carried out to determine the effects of embalming and to study the more edematous nature of the surgical specimen.

Thirty adult white rats were used to study the effects of embalming on the stomach. Details of such a study are published elsewhere.[1] It was found that embalming had very little or no effect on the weight of the stomach. Thirty other rats were used to evaluate the effects of gastric resection on the weight of the stomach. Fifteen of these rats were anesthetized; total gastrectomy was performed promptly, and the stomachs were weighed and measured. The other 15 rats were anesthetized, and their stomachs were irritated by pinching with forceps at five-minute intervals for a period of one to two hours. This was done for the purpose of simulating trauma to the stomach which may occur during gastric resection. Total gastrectomy was then performed on these 15 rats, and their stomachs were weighed and measured. The weights and measurements of these two groups of stomachs were then compared with normals for the rat issued by the Wistar Institute. It was found that the stomachs that had been removed surgically without trauma weighed, on the average, 12% less than the normals recorded by the Wistar Institute. The stomachs that were traumatized for one to two hours prior to removal appeared more edematous and weighed, on the average, 7% more than the standard for the corresponding rat (Fig. 4).

From these observations it appeared that a stomach that was traumatized for a time and then removed surgically would weigh more than a stomach obtained post mortem. It also appeared that a stomach that was handled considerably during surgical removal would weigh more than one that was handled little. It was thought that these differences would cause some error in the method, but such discrepancies were not considered of major significance, since variations of this type would be relatively uniform in the operating room.

By use of the first graph (Fig. 2), a table was then made for ease in estimating the amount of stomach removed at the time of operation for duodenal ulcer. The Table is constructed so that the percentage of stomach removed is easily determined from

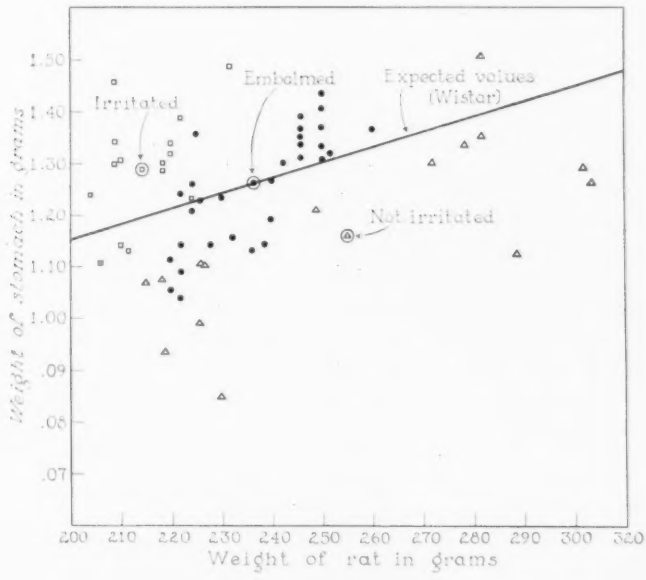


Fig. 4.—Graph showing effects of embalming and of manipulation on interpretation of measurements designed to calculate percentage of stomach removed.

*Table Used in Calculation of Percentage of Stomach Removed*

| Estimated Percentage of Stomach Removed | Thickness of Muscularis, Mm. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 4.5 | 5.0 |
| | Weight of Excised Portion of Stomach, Gm. | | | | | | | | |
| 60 | 54 | 81 | 108 | 134 | 161 | 188 | 215 | 242 | 269 |
| 61 | 57 | 85 | 114 | 142 | 170 | 199 | 228 | 256 | 284 |
| 62 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 |
| 63 | 63 | 95 | 126 | 158 | 189 | 221 | 252 | 284 | 316 |
| 64 | 66 | 99 | 132 | 166 | 198 | 232 | 265 | 298 | 331 |
| 65 | 69 | 104 | 139 | 174 | 208 | 243 | 278 | 312 | 347 |
| 66 | 72 | 109 | 145 | 181 | 218 | 254 | 290 | 326 | 362 |
| 67 | 76 | 113 | 151 | 189 | 226 | 265 | 302 | 340 | 378 |
| 68 | 79 | 118 | 157 | 197 | 236 | 275 | 315 | 354 | 394 |
| 69 | 82 | 123 | 164 | 204 | 245 | 286 | 327 | 368 | 409 |
| 70 | 85 | 128 | 170 | 212 | 255 | 298 | 340 | 382 | 425 |
| 71 | 88 | 132 | 176 | 220 | 264 | 308 | 352 | 396 | 440 |
| 72 | 91 | 137 | 182 | 228 | 273 | 319 | 365 | 410 | 456 |
| 73 | 94 | 141 | 189 | 236 | 283 | 330 | 377 | 424 | 472 |
| 74 | 97 | 146 | 195 | 244 | 292 | 341 | 390 | 438 | 487 |
| 75 | 101 | 151 | 201 | 252 | 301 | 352 | 402 | 453 | 503 |
| 76 | 104 | 156 | 207 | 259 | 311 | 363 | 415 | 467 | 518 |
| 77 | 107 | 160 | 214 | 267 | 320 | 374 | 427 | 481 | 534 |
| 78 | 110 | 165 | 220 | 275 | 329 | 385 | 440 | 495 | 550 |
| 79 | 113 | 170 | 226 | 282 | 339 | 396 | 452 | 508 | 565 |
| 80 | 116 | 174 | 232 | 290 | 348 | 407 | 465 | 523 | 581 |

the weight of the resected piece and the thickness of the muscularis (Table). Obviously, this method is not applicable if there is any significant pathologic change in the stomach itself, such as a gastric ulcer.

For practical purposes, this Table is kept in the laboratory of surgical pathology. When the resected part of the stomach is brought to the laboratory, the surgical pathologist removes all fat and weighs the specimen. He then measures the thickness of the muscularis at the upper line of resection. With these measurements the percentage of the stomach removed is determined from the Table. This percentage may be reported to the operating surgeon within minutes. If more of the stomach need be removed, this can be accomplished before the anastomosis is begun.

Clinical experience will not be reported at this time except to say that application of this method of estimating the percentage of stomach removed at the time of partial gastrectomy has given consistent results except when long-standing gastric obstruction has resulted in gastric dilatation following an initial period of hypertrophy of the gastric musculature.


## Summary

A method is described whereby the percentage of the stomach removed at resection can be calculated on the basis of the weight of the resected specimen and the thickness of the muscularis measured at the upper edge of the surgical specimen. There is an estimated error of 6% in the method. A Table is used to simplify the calculations.


Section of Surgical Pathology (Dr. Dockerty).

## REFERENCE

1. Donaldson, H. H.: The Rat: Data and Reference Tables for the Albino Rat (Mus Norvegicus Albinus) and the Norway Rat (Mus Norvegicus), Ed. 2, Memoirs of the Wistar Institute of Anatomy and Biology, No. 6, Philadelphia, 1924, p. 215.

## DISCUSSION

DR. CECIL G. MCEACHERN, Fort Wayne, Ind.: This study of measurements of the resected portion of stomach in cases of duodenal ulcer was carried out a few years ago, and since that time has been used satisfactorily in several institutions. Since Finsterer, in 1918, first pointed out the relationship between an adequate resection and the end-result, there has been no accurate method of measurement of the resected portion of stomach.

The various methods previously utilized, namely, measurement determination of weight, determination of volume, and linear measurements, have left much to be desired. The simplicity of application of this method and the rapidity with which it can be applied should ensure an adequate resection.

The method also provides a more accurate basis for the study of the comparative methods of gastric resection. I should like to congratulate Dr. Heinrich on his fine presentation of a subject which has many variables.

DR. EDWARD S. JUDD, Rochester, Minn.: I am very sorry Dr. Priestley was unable to be here today, for he is greatly interested in this field, as you know. He asked me to say a word in his absence.

I have been much interested in Dr. Heinrich's method. Dr. Heinrich and I happened to be working together when he conceived this idea. He asked me whether I thought it would work. I remember discussing it with Dr. Wangensteen, at our University, at that time. Dr. Wangensteen was convinced it would not work, because, he said, one could not determine from a piece of stomach that is now outside the body just how much stomach remains within the body. It is my understanding that after Dr. Heinrich's work, however, Dr. Wangensteen has become somewhat convinced; perhaps Dr. Wangensteen will have a few words to say about that at this meeting.

Dr. Heinrich stressed the laboratory implications of the method. My colleagues and I have been much impressed with the clinical aspects. After all, we as surgeons have been in the habit of recording what we think we are removing, and perhaps we are embarrassed at times when other, more critical observers see the specimen, or perhaps the result.

The previous demand for resection of at least three-fourths of the stomach may be based on invalid conclusions. Some surgeons, as you all know, say that three-quarters of the stomach is too much to remove, and they remove only two-thirds. If the surgeon relies simply on his guess, the estimate does not mean a great deal scientifically.

At present, more and more is being heard about hemigastrectomy and vagotomy. There, again, if the amount of stomach removed at each operation is simply the surgeon's rough estimate, removal of the same amount of stomach as indicated by these estimates does not have any uniform effect on clinical and scientific results.

As Dr. Heinrich has pointed out, if there is marked obstruction of the stomach, with great thickness of the wall, the percentage of error with the method he has described will be somewhat increased. At the Mayo Clinic we are using this method, however, and the formulae are available in both our surgical pathology laboratories. It seems to us that we now have a method that is much more accurate than the surgeon's estimate.

This method has a distinct clinical use in assessing the patient who has a recurrent ulcer. If we know exactly how much stomach was taken out the first time, that information may guide us definitely in the approach at a second operation.

DR. WESTON A. HEINRICH, Evansville, Ind.: I would like to thank Dr. McEachern and Dr. Judd for their discussion of this subject.

# Peptic Ulcer Associated with Tumors of the Pancreas

HARRY A. OBERHELMAN Jr., M.D.; THOMAS S. NELSEN, M.D., and LESTER R. DRAGSTEDT, M.D., Ph.D., Chicago

The association of progressive and recurrent peptic ulceration with non-insulin-producing islet-cell tumors of the pancreas was first observed by Zollinger and Ellison in 1955.[1] In 1956 [2] Ellison reviewed 24 cases of ulcerogenic tumors of the pancreatic islets from various sources and characterized this new clinical syndrome. It consisted of a hypersecretion of gastric juice with progressive peptic ulceration, recurring despite adequate medical and surgical therapy, and the presence of non-insulin-producing islet-cell tumors of the pancreas. The ulcers were frequently located in atypical sites, such as the jejunum and distal duodenum, as well as the esophagus, stomach, and duodenal bulb. Symptoms were usually referable to the ulcer and its complications and frequently resulted in death. The majority of these islet-cell tumors were considered malignant and in most instances consisted of cells devoid of beta granules, suggesting that they might be of alpha-cell origin. Since glucagon, or hyperglycemic-glycogenolytic factor, is thought to arise from the alpha cells of the pancreatic islets, Zollinger and Ellison suggested that glucagon might be the ulcerogenic factor.

More recently Donaldson, vom Eigen, and Dwight [3] reported on a similar case in which an extreme gastric hypersecretion was demonstrated over a period of more than two years before recognized clinical manifestation of peptic ulceration appeared. They reviewed the literature, summarized 21 previously reported cases, and made the observation that 6 of the 21 cases were characterized by the finding of multiple endocrine abnormalities. However, in none of the 15 remaining cases was evidence adequate to warrant the assumption that abnormalities of multiple endocrine organs were not present. Fisher and Flandreau in 1957 [4] reported the clinical and pathologic findings in a patient with multiple peptic ulcerations associated with hyperplasia of the parathyroids, adrenal cortices, amphophils and basophils of the anterior pituitary, and alpha-cell tumors of the pancreatic islets. In their patient the initial symptoms were due to hyperparathyroidism rather than peptic ulcer. They suggested that ulcer formation in patients with this syndrome might be related to the secretions of all or several of the involved endocrine organs.

Although much has been written about this clinical entity since Zollinger and Ellison's report, there are still many difficult and perplexing aspects, not only in the etiology of this syndrome but in establishing a diagnosis and effecting adequate treatment. It is the purpose of this report to describe the clinical and pathologic findings in three additional cases emphasizing the various problems encountered in patients with intractable-ulcer diathesis.

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## Report of Cases

CASE 1.—This 52-year-old streetcar conductor was in good health until 1953, when he developed postprandial epigastric distress. A diagnosis of duodenal ulcer was made and the patient placed on medical management. He remained fairly well until April, 1954, when his ulcer perforated. Emergency laparotomy was performed, with simple

closure of the perforation. He was again placed on strict medical management, with relief of symptoms until June, 1954. At this time he suffered a massive gastrointestinal hemorrhage, requiring 19 units of blood. A subtotal gastrectomy was performed. Three months later he developed homologous serum jaundice, from which he recovered uneventfully. In October, 1954, his ulcer distress recurred and a stomal ulcer was demonstrated. He underwent a transthoracic vagotomy but in less than two months noted a recurrence of epigastric distress accompanied by severe diarrhea. A diagnosis of recurrent stomal ulcer and gastrojejunocolic fistula was made. In September, 1955, surgical repair of the fistula and a further gastric resection were performed, leaving the patient with less than 20% of his original stomach. He remained well until January, 1957, when his epigastric distress again recurred. Two months prior to admission x-rays revealed a recurrent stomal ulcer, but, despite medical management, he complained of severe epigastric pain. During this time he developed marked anorexia and lost approximately 20 lb. in weight.

On admission to The Universty of Chicago Clinic in June, 1957, physical examination revealed a well-developed, thin white man, showing evidence of recent weight loss. There were numerous well-healed scars in the upper abdomen and generalized upper abdominal tenderness. The hemoglobin, white cell count, urinalysis, serum electrolytes, and serum calcium, phosphorus, and glucose were within normal limits. Plasma proteins were slightly diminished, but the NPN and both alkaline and acid phosphatase were normal. Liver function studies revealed no evidence of liver disease. Three 12-hour night gastric secretion studies yielded, respectively, 27, 25, and 31 mEq. of free HCl. Insulin tests were interpreted as showing complete section of the vagus nerves. Gastroduodenal x-ray studies confirmed the presence of a large, 1.25 cm. stomal ulcer (Fig.1). Following extensive studies a preoperative diagnosis of a non-insulin-producing islet-cell tumor of the pancreas was made. Several days prior to surgery the patient complained of intermittent pain in the left lower quadrant.

On June 20, 1957, an exploratory laparotomy was performed, at which time a large perforated stomal ulcer was found. The pancreas was carefully palpated, but no definite masses were noted. However, a hard lymph node in the region of the head of the pancreas was found after mobilizing the duodenum. Both frozen and permanent sections of this node showed metastatic carcinoma compatible with an islet-cell tumor of the pancreas (Fig. 2*A* and *B*). Since the majority of tumors previously reported were located in the body and tail of the pancreas, it was decided to resect this portion in hopes of removing the primary tumor.

Fig. 1.—Roentgenogram of upper gastrointestinal tract showing large stomal ulcer crater.

The stomal ulcer was also removed with a narrow rim of stomach and a gastrojejunostomy constructed.

Postoperatively the patient did well for two weeks, but then fever and purulent drainage from the abdominal drain site developed. He complained of both upper and lower abdominal pain and had one episode of hematemesis, followed by tarry stools. A dye injection of the draining sinus revealed a connection with the jejunum and gastrojejunal anastomosis. X-rays of the stomach again revealed recurrent marginal ulceration. He was placed on strict ulcer management. Numerous 12-hour night gastric secretion studies showed a return of his hypersecretion to preoperative levels. In view of his poor clinical response to medical therapy, x-irradiation of the gastric remnant was given. He showed some improvement following x-ray therapy, with spontaneous closure of the abdominal fistula, and was discharged from the hospital on Aug. 3, on strict medical management.

While at home the patient continued having some abdominal distress. In September, 1957, he was readmitted for further evaluation. Laboratory data were essentially normal on this admission except for a slight elevation in the alkaline phosphatase. Stools were consistently positive for occult blood, and, although the 12-hour night gastric

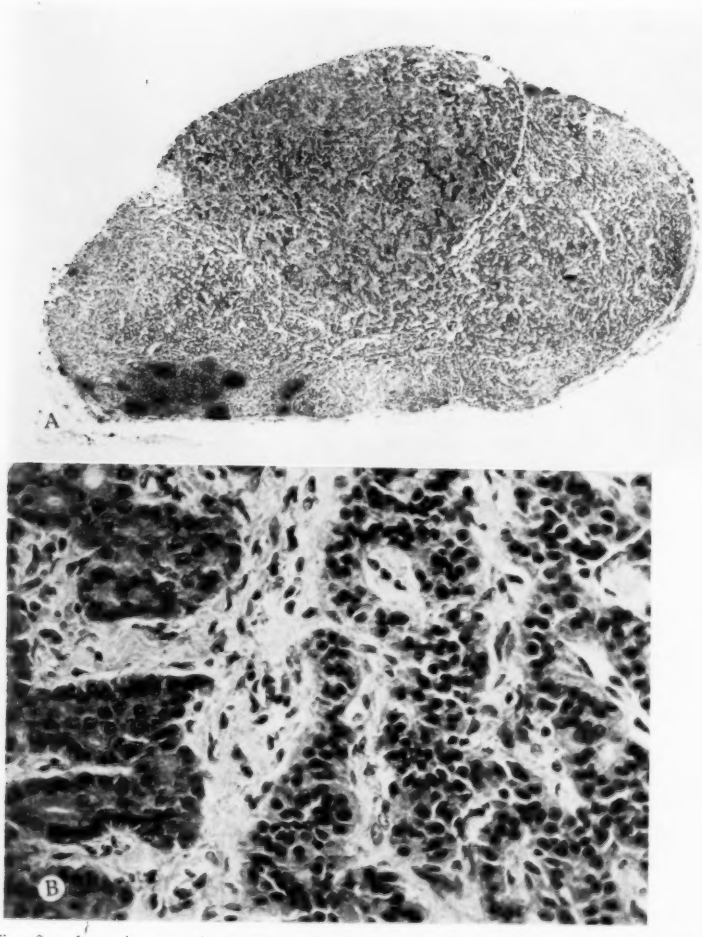



Fig. 2.—*A*, peripancreatic lymph node almost completely replaced by metastatic islet-cell carcinoma. H & E; ×20.

*B*, high-power appearance of tumor in lymph node showing its glandular pattern. H & E; ×500.

secretions revealed no free acid, there were 5 to 20 clinical units of free acid in the morning fasting specimens and a moderate response in acidity to histamine stimulation. Calcium balance studies were performed to study parathyroid function, but no evidence of hyperparathyroidism was evident. X-ray studies of the stomach again revealed a large stomal ulcer with a gastrojejunocolic fistula demonstrated on barium enema (Figs. 3 and 4).

It was elected to remove the remaining pancreas, since a carcinomatous peripancreatic lymph node had previously been found. On Oct. 15, 1957, exploration was again carried out and the large stomal ulcer visualized. The head of the pancreas and the duodenum were resected, anastomosing the common duct with the distal end of the duodenum. In view of the magnitude of this procedure, the ulcer and gastrojejunocolic fistula were left intact. Microscopic sections of the specimen revealed what was interpreted as being a non-insulin-producing islet-cell tumor arising in ectopic pancreatic tissue in the wall of the duodenum near the duct of Santorini (Fig. 5 *A* and *B*). Special stains using the Gomori technique failed to reveal alpha cell granules in the tumor cells.

The patient made an uneventful recovery and required about 20 units of isophane insulin U. S. P. (NPH insulin) daily. He was completely free of ulcer pain during the postoperative period. Stools were bulky and soft, denoting pancreatic insuffici-

Fig. 3.—Roentgenogram of upper gastrointestinal tract showing a large recurrent stomal ulcer crater.

ency, and he was given Viokase, a whole-pancreas preparation, by mouth and cyanocobalamin (vitamin $B_{12}$) parenterally. Postoperative 12-hour night secretion studies showed no free acid, and there was no acid in response to histamine. He was discharged on the 39th postoperative day.

The patient was readmitted for further study in January, 1958, three months following the total pancreatectomy. He had remained asymptomatic and had gained 18 lb. in weight. The 12-hour night gastric secretion again showed no free acid, but a slight response to histamine stimulation was observed. X-rays of the gastrointestinal tract showed complete healing of the stomal ulcer and closure of the gastrojejunocolic fistula (Fig. 6).

*Comment*

This is one of the first cases in which total pancreatectomy with removal of a non-insulin-producing islet-cell carcinoma without further gastric resection or vagotomy has resulted in a definite decrease in gastric secretion with healing of the marginal ulcer and closure of the gastrojejunocolic fistula. It is too early to draw definite conclusions, but the clinical remission strongly suggests that the ulcerogenic factor had its origin in the islet-cell tumor of the pancreas. This factor is neither nervous nor antral in origin, since the hypersecretion of gastric juice remained unchanged after vagotomy and gastric resection. It has been suggested by some that glucagon might be this ulcerogenic factor; however, experimental studies in Heidenhain pouch dogs in our laboratory and elsewhere have failed to demonstrate stimulation of gastric secretion as a property of this substance. Our thoughts were directed to the possibility that this humoral factor might be similar to, or indeed be, gastrin, the hormone of the gastric antrum.

Previous studies from this laboratory[5,6] have demonstrated that the antral or hormonal phase of gastric secretion mediated by gastrin can be inhibited by the intravenous administration of pancreatic secretin* or by promethazine (Phenergan), a

* Preparations of secretin were secured from Eli Lilly & Company and "contained 10 clinical units of pancreatic secretin per cubic centimeter, one clinical unit being equal to 1 dry dog unit."[6]

Fig. 4.—Barium-enema roentgenogram showing gastrojejunocolic fistula.

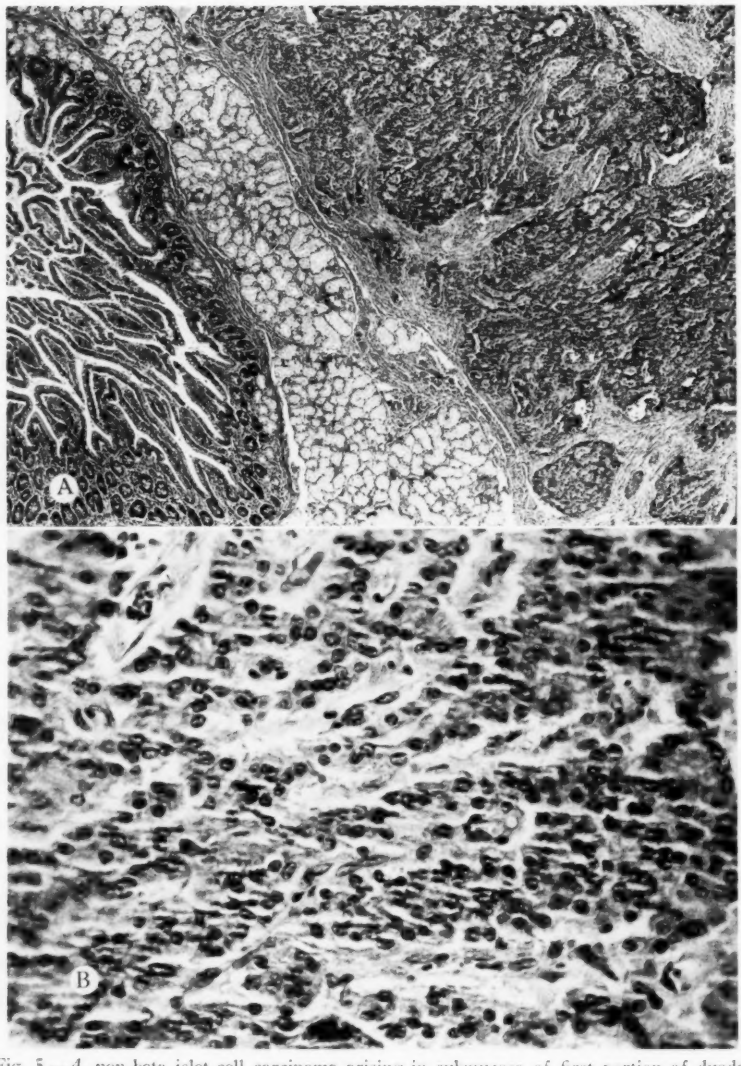



Fig. 5.—*A*, non-beta islet-cell carcinoma arising in submucosa of first portion of duodenum near duct of Santorini. H & E; × 55.
*B*, high-power appearance of tumor composed of nests of cells devoid of beta granules. H & E; × 500.

potent antihistaminic drug. However, attempts to inhibit gastric secretion in this patient by the administration of these agents were unsuccessful. Further clinical and experimental studies are necessary to identify the nature of this ulcerogenic factor.

The significance of the abnormal changes in the islets of Langerhans of this patient's pancreas, consisting of proliferation and hyperplasia, is also not clear (Fig. 7). Acid-alcohol extracts of the resected pancreas were prepared and injected into experimental animals. There was no observable effect on gastric secretion. It would appear that the humoral ulcerogenic factor came from the islet-cell tumor, and not from the

Fig. 6.—Roentgenogram showing healing of stomal ulcer following total pancreatectomy.

abnormal islets of the pancreas proper. No extracts of the tumor itself were made because of its small size.

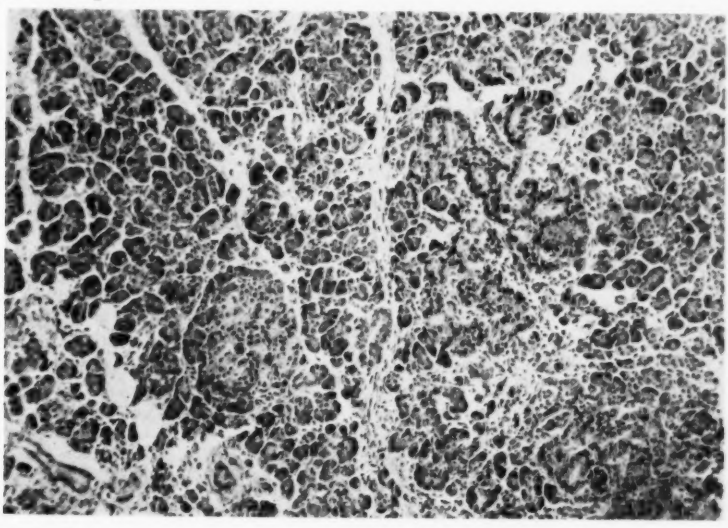
The excellent recovery of this patient following total pancreatectomy indicates that modern methods of treating pancreatic insufficiency are fairly adequate and justify this radical procedure for the control of gastric hypersecretion if definite histologic evidence of islet-cell tumor is established.

In addition, since many of these islet-cell tumors are malignant and frequently multiple in origin, total pancreatectomy is the only method of treatment which offers any chance for permanent remission.

CASE 2.—This 37-year-old Negro galvanizer was first seen at The University of Chicago Clinics in February, 1950, with the chief complaint of ulcer distress of five years' duration, with inability to obtain relief from medical management. There was no history of hemorrhage or perforation, but night pain was severe. Physical examination and routine laboratory work were within normal limits. X-rays of the stomach revealed a 7 mm. duodenal ulcer crater, and the 12-hour nocturnal gastric secretion measured 22 mEq.

A transabdominal vagotomy and posterior gastroenterostomy were performed, with relief of symptoms. Postoperatively the response to insulin hypoglycemia was negative. He remained well

Fig. 7.—Photomicrograph of pancreas proper showing papillary proliferation and hyperplasia of islets of Langerhans.



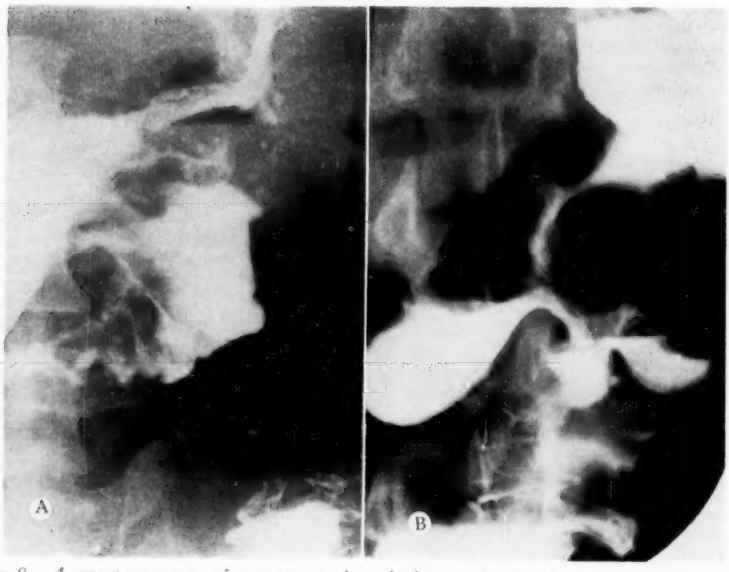



Fig. 8.—*A*, roentgenogram of upper gastrointestinal tract showing large stomal ulcer crater. *B*, roentgenogram of upper gastrointestinal tract showing recurrent stomal ulcer crater.

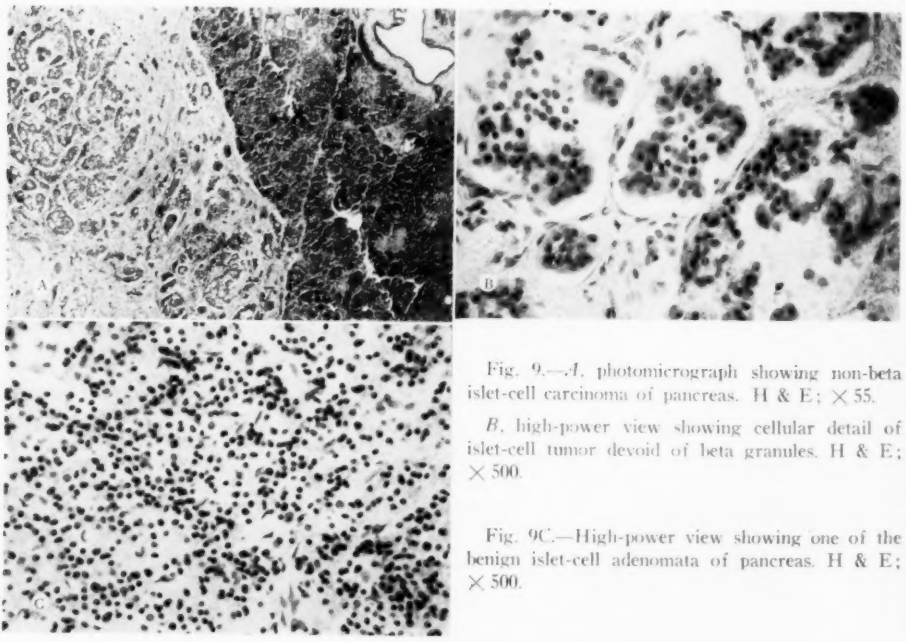



Fig. 9.—*A*, photomicrograph showing non-beta islet-cell carcinoma of pancreas. H & E; × 55.

*B*, high-power view showing cellular detail of islet-cell tumor devoid of beta granules. H & E; × 500.

Fig. 9C.—High-power view showing one of the benign islet-cell adenomata of pancreas. H & E; × 500.

until June, 1956, at which time epigastric distress relieved by food or alkali returned. He was readmitted to the hospital on Aug. 19, 1956, for further study. Physical examination and the usual laboratory evaluation were not remarkably abnormal, except that the stools gave a 3+ positive reaction for occult blood. Gastroduodenal x-rays showed a large stomal ulcer (Fig. 8*A*). Twelve-

hour nocturnal gastric secretion measured 31 mEq., and the insulin test was again negative. The patient was treated by x-radiation to the gastric fundus, methscopolamine (Pamine), and antacids. Two weeks after the onset of the radiation therapy he required readmission for what was considered radiation gastritis. This subsided rapidly, and re-evaluation in the outpatient department showed healing of the ulcer by x-ray in August, 1956, although he required methscopolamine for complete relief of his distress.

The patient was readmitted as an emergency on Feb. 26, 1957, with the complaints of severe epigastric distress, vomiting, and hematemesis of 12 hours' duration. Physical examination revealed the presence of epigastric tenderness without rigidity or decrease in bowel sounds. Urinalysis revealed 4+ reduction and a 4+ reaction for acetone on admission. Later examinations were negative for sugar and acetone, but showed doubly refractile fat in casts and cells. Admission blood count, electrolytes, and A/G ratio were within normal limits. The NPN was 33 mg. %, and the fasting blood sugar was 77 mg. %. The 12-hour nocturnal gastric secretion was 94 mEq., and x-rays again demonstrated a large stomal ulcer (Fig. 8*B*).

The initial treatment consisted of gastric aspiration, followed by administration of milk and powders hourly. On March 7, 1957, a two-thirds gastric resection with excision of the large stomal ulcer was performed. No pancreatic abnormality was identifiable. Histologic examination of the removed specimen showed spectacular hypertrophy and hyperplasia of the gastric glands, primarily of the parietal cells.

Postoperatively, the patient developed pneumonia and a condition resembling the milk-alkali syndrome, with elevation of the NPN to 110 mg. % and the Ca to 13.1 mg. %, with normal phosphorus, phosphatases, and proteins. It was the opinion of the medical consultants that this case represented chronic renal disease with superimposed hyperparathyroidism. The pneumonia cleared, and the NPN returned toward normal, dropping to 84 mg. % on the 10th postoperative day. Plans were made for surgical parathyroidectomy. However, massive hematemesis occurred, and, in spite of multiple transfusions, he died a few hours later.

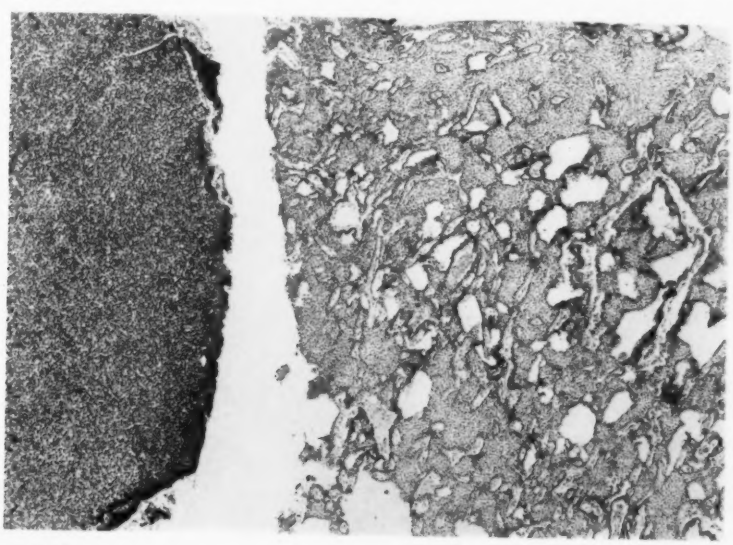
### *Autopsy Findings*

Stomach and Intestines: The gastrointestinal tract was massively dilated by intraluminal clotted blood. A severe necrotizing peptic esophagitis was demonstrable. The submucosa of the upper gastrointestinal tract was hemorrhagic and congested.

Pancreas: This organ appeared grossly normal. The sections demonstrated a 2×2×3 mm. islet-cell carcinoma of the head of the pancreas and other adenomata of islet origin, the largest of which was 5 mm. in diameter (Figs. 9*A* and *B*; 9*C*).

Parathyroids: Of the three glands identified, the left lower parathyroid weighed 7.5 gm., the right lower gland weighed 6.3 gm., and the third was twice the normal size. Sections showed adenomatous hyperplasia and hypertrophy (Fig. 10).

Fig. 10.—Photomicrograph of parathyroid showing adenomatous hyperplasia and hypertrophy. H & E; ×60.



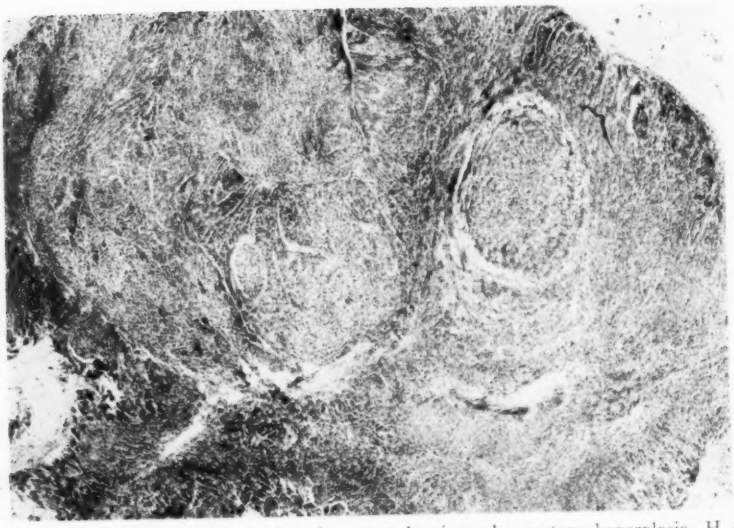


Fig. 11.—Photomicrograph of adrenal cortex showing adenomatous hyperplasia. H & E; × 22.

Adrenals: The right gland weighed 13.5 gm. and the left 11.5 gm. Histologic examination revealed adenomatous cortical hyperplasia bilaterally (Fig. 11).

Pituitary: Sections demonstrated a basophilic adenoma, basophilic invasion of the posterior lobe, and diffuse eosinophilic hyperplasia (Fig. 12).

Testes: Evidence was present on the section for active, but diminished, gametogenesis. The individual tubules were atrophic and widely separated by a loose collagenous stroma. The interstitial cells were pale and indistinct (Fig. 13).

Kidneys: The right kidney weighed 160 gm.; the left, 150 gm. Gross and microscopic evidence for nephrolithiasis and nephrocalcinosis was present, but the over-all appearance was compatible with good renal function (Fig. 14).

Fig. 12.—Photomicrograph of hypophysis showing large basophilic adenoma. H & E × 53.

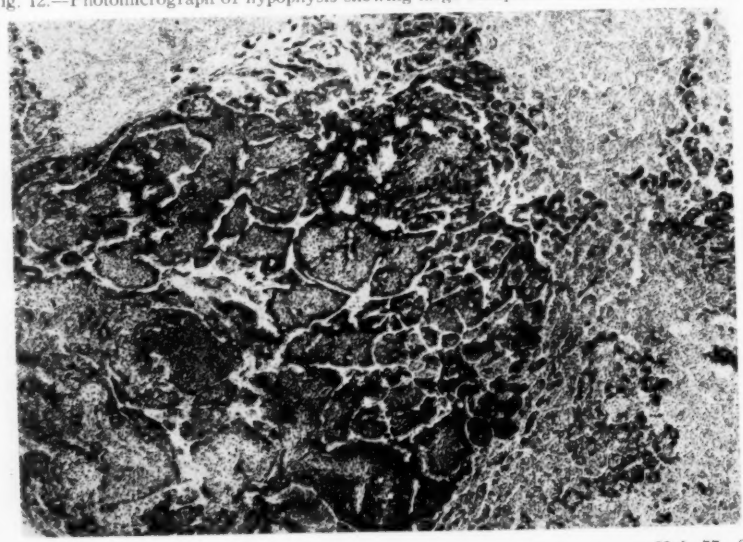
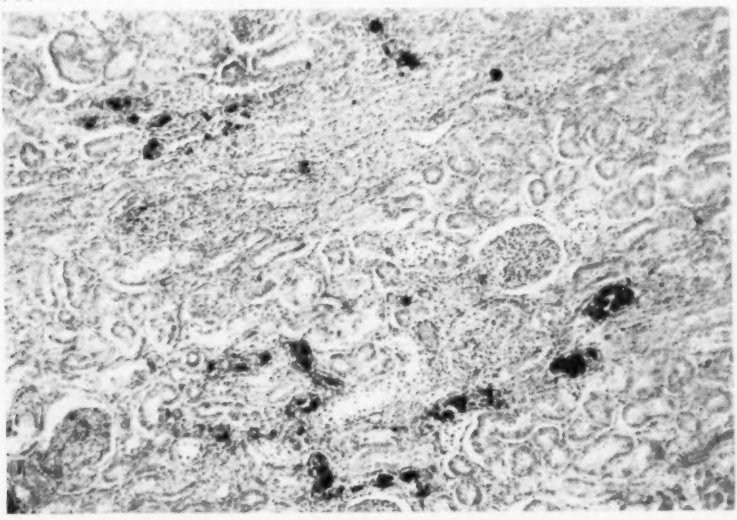


Fig. 13.—Photomicrograph of testes showing atrophy, indistinct interstitial cells, and diminished spermatogenesis. H & E.; × 120.

*Comment*

The findings in this patient represent another unusual cause of intractable peptic ulcer, namely, multiple endocrine adenomata. The negative response to insulin hypoglycemia and the failure of complete vagotomy to heal the peptic ulcer indicate that the source of the gastric hypersecretion was not vagal but hormonal. This patient's hyperparathyroidism is well documented by laboratory and histologic evidence. As mentioned earlier, several of Zollinger and Ellison's patients with intractable peptic ulceration associated with non-beta islet-cell tumors of the pancreas showed other endocrine gland abnormalities.

Fig. 14.—Photomicrograph of kidney showing calcium deposition in renal tubules. von Kossa stain; × 125.



Fisher and Flandreau have suggested that the ulcer formation in patients with multiple endocrine adenomata might be caused by hypersecretion from one or several of the involved glands and pointed out that the testicular atrophy noted in their patient may have indirectly produced excessive secretion of various tropic hormones from the anterior lobe of the hypophysis. It seems significant that only the thyroid and testes, of all the pituitary-target glands, showed no evidence of excess stimulation. In our patient the testes were hypoplastic, with indistinct interstitial cells. However, spermatogenesis in diminished amount was present. Direct evidence implicating pituitary hyperfunction as the primary etiologic agent is at this time lacking. In fact, one cannot be certain whether the hypersecretion of gastric juice in these cases was due to the pancreatic islet-cell tumor or hyperparathyroidism or both. Demonstration of a specific substance from the parathyroid glands which provokes gastric secretion has also not been accomplished.

Case 3.—This 64-year-old man was in good health until seven years ago, when he devedoped burning, postprandial epigastric pain. A diagnosis of cholelithiasis and duodenal ulcer was made and the patient treated conservatively. In September, 1953, the patient underwent cholecystectomy. The duodenal ulcer was visualized at operation and a pancreatic biopsy specimen obtained. He remained well for seven months, only to develop severe right upper quadrant and epigastric pain. X-rays revealed an active duodenal ulcer, and in August, 1954, a gastric resection was performed. However, he continued to complain of epigastric distress with radiation of pain to the back.

He entered The University of Chicago Clinics in November, 1954, at which time physical examination was essentially negative except for moderate epigastric tenderness. Hemoglobin, white cell count, urinalysis, serum electrolytes, NPN, serum proteins, and serum bilirubin were within normal limits. The 12-hour nocturnal gastric secretion yielded 36 mEq. of free hydrochloric acid. X-rays of the stomach revealed a marginal ulcer. On Dec. 1, 1954, an exploratory laparotomy was performed and the ulcer visualized. An enteroenterostomy was also found below the gastrojejunal anastomosis. This was taken down and a transabdominal supradiaphragmatic vagotomy performed. Following recovery, the patient obtained complete relief of his ulcer symptoms until February, 1955, when he again noted recurrent severe epigastric pain. Gastric secretion studies revealed 26 mEq. of free hydrochloric acid in the 12-hour nocturnal collection and a negative response to insulin hypoglycemia. X-rays of the stomach revealed a recurrent stomal ulcer (Fig. 15). The patient was again placed on strict medical management. However, the relief of symptoms was temporary, and he continued to have intermittent episodes of epigastric pain. Further gastric secretory studies in September, 1956, revealed no change in his 12-hour nocturnal secretion, and the acid response to insulin hypoglycemia was difficult to evaluate because of his high fasting secretion. He received x-ray therapy to the gastric fundus, from which he received only slight relief. A review of the pancreatic biopsy specimen taken in September, 1953, showed a diminution in the number of islet cells but no evidence of tumor or pancreatitis. The patient continued to have intermittent ulcer distress, which was only partially relieved by the intake of milk, cream, and powders, and was again admitted to the hospital in October, 1957. X-rays of the stomach again showed a large marginal ulcer (Fig. 16). Twelve-hour nocturnal gastric secretion findings

Fig. 15.—Roentgenogram of upper gastrointestinal tract showing recurrent stomal ulcer crater.

Fig. 16.—Roentgenogram of upper gastrointestinal tract showing large recurrent marginal ulcer crater.

varied between 24 and 100 mEq. of free hydrochloric acid. Calcium balance studies were also performed in studying parathyroid function. A persistently low serum phosphorus suggested hyperparathyroidism, but other special studies failed to confirm the diagnosis. In view of his persistent gastric hypersecretion, surgery was again advised. An exploratory laparotomy was done on Nov. 14, 1957. A large stomal ulcer was resected along with 50% of the gastric remnant, leaving the patient with about 10%-15% of his original stomach. The pancreas was carefully explored, but no evidence of tumor could be found. Four biopsy specimens were obtained from various portions of the pancreas, none showing gross or microscopic evidence of pancreatic abnormality. The duodenal stump was also exposed and appeared moderately dilated, as though the proximal end might represent residual gastric antrum. There was also a narrowing of the second portion of the duodenum, probably the reason for dilatation of the proximal stump. This distended portion of the duodenal stump was resected and another closure performed just above the ampulla of Vater.

Postoperatively, gastric secretory studies showed an absence of free hydrochloric acid in the 12-hour nocturnal secretion. He has remained entirely free of ulcer symptoms since surgery, and recent x-rays of the stomach reveal a normal functioning gastroenterostomy.

*Comment*

This case is presented to illustrate the difficulties in making the diagnosis of an islet-cell tumor of the pancreas. In spite of a persistent hypersecretion of gastric juice after high subtotal gastrectomy and vagotomy, no evidence of tumor or pancreatic abnormality could be found. The completeness of the vagotomy was confirmed by a negative response to insulin hypoglycemia. In this case it is intriguing to speculate that chronic distention of the duodenal stump resulted in the release of an intestinal hormone which stimulated the parietal cells of the gastric stump, resulting in a continuous hypersecretion of gastric juice. Very little is known concerning the intestinal phase of gastric secretion, but experimental studies in dogs suggest it is mediated by a humoral agent. Studies also show that the intestinal phase of secretion is augmented by the passage of neutral or alkaline food into the duodenum, in contrast to acid food.[7] Thus, a possible mechanism is suggested by this patient, in whom regurgitation of alkaline secretions and food into the duodenal stump and increased tension, as a result of the distal stenosis, have resulted in hypersecretion of gastric juice similar to what occurs after antrum-exclusion procedures.

Greenlee[5] also noted the effect of pancreatic secretin on the intestinal phase of secretion in dogs and observed little or no inhibitory action, in contrast to its effect on the gastric phase of secretion. Attempts to inhibit the continuous hypersecretion of gastric juice in this patient by the administration of pancreatic secretion proved unsuccessful. This finding lends support to the above hypothesis that an augmented intestinal-phase secretion is present. Certainly, if the marked decrease in gastric secretion persists, one must accept the above explanation as being reasonable. Thus, one must consider the possibility that there are

other causes of persistent gastric hypersecretion which must be explored in addimotion to non-insulin-producing islet-cell tumors of the pancreas with or without other endocrine abnormalities.

## Summary

The finding of intractable-ulcer diathesis in a patient with a non-insulin-producing islet-cell tumor of the pancreas and in a second patient with multiple endocrine adenomata is presented. Whether these two conditions represent separate clinical entities is not known. There is definite but limited evidence to support the concept that the ulcerogenic factor arises from the nonbeta islet-cell tumors of the pancreas. It is also true that patients with proved pancreatic islet-cell tumors have not been studied adequately to exclude other endocrine disease. In many of the previously reported cases of multiple endocrine adenomata, acromegaly was present, indicating pituitary hyperfunction. This observation, coupled with the striking pituitary lesions found in our patient, suggests to us that within the hypophysis, or perhaps the hypothalamus, may rest the primary cause of this complex syndrome of multiple endocrine abnormalities. Wermer, however, in 1954 [8] suggested that the syndrome of multiple endocrine adenomatosis with peptic ulceration is caused by an inherited genetic disturbance. The persistent and marked gastric hypersecretion found in such cases probably stems directly from a hormone produced by the pancreatic islet-cell tumors. At the present time we have no evidence that the hypophysis, parathyroids, thyroid, adrenals, or gonads can produce gastric hypersecretion with peptic ulceration. It seems certain that increasing awareness of multiple endocrine adenomata as a cause of intractable-ulcer diathesis and more complete investigation, both clinical and pathologic, will augment the number of reported cases and our knowledge of this problem.

The third case reported above emphasizes that other (intestinal) factors may result in intractable-ulcer disease.

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## DISCUSSION

DR. EDWIN H. ELLISON, Columbus, Ohio: It has been exciting to hear Drs. Oberhelman, Nelsen, and Dragstedt report three cases of ulcerogenic tumor. Their suggestions as to some of the mechanisms involved were extremely interesting, and I would like to hear how the cases eventually turn out.

This may be an appropriate time, Dr. Jenkins, to present the latest report on the Ulcerogenic Tumor Registry. Unfortunately, the majority of the new cases are still found by the autopsy surgeon, and not the clinical surgeon.

To date, we have summarized a total of 72 cases. Of these, two out of three had tumors located in the body or tail of the pancreas, and one out of three tumors were of low-grade malignancy. On the basis of clinical case histories, only one-half of the metastatic lesions functioned, a finding which is not unlike that in insulin-producing tumors.

One-third of the tumors have been multiple, presenting a serious problem in management. Approximately 10% are located in aberrant positions, including the antrum, the duodenal wall, and the splenic hilus. It would seem that they can develop in aberrant pancreas no matter where it occurs.

Of the tumors located in the pancreas, approximately 15% could not be identified by palpation. Dr. Keith Grimson has reported one such case in which the tumors were not evident until the pancreas was examined microscopically.

Diagnosis, therefore, continues to be an important problem. Peptic ulcerations found in unusual locations, such as the upper jejunum, or ulcerations recurring soon after an adequate operative procedure for ulcer should give rise to a high degree of suspicion. In addition, patients found to produce over 100 mEq. of free HCl during a 12-hour period must be screened for ulcerogenic islet-cell tumors. X-ray findings may be helpful. A commoner finding is marked hypertrophic gastritis or a duodenal ileus with or without polypoid changes in the duodenal wall.

Finally, the multiple endocrine tumor syndrome has occurred in about 25% of the cases. These tumors may be functioning, as well as the islet in the pancreas. There have been mixed tumors with insulin-producing characteristics. There have also been cases of active hyperparathyroidism and hyperpituitarism, as well as ulcerogenic tumors, all functioning simultaneously.

As you know, the mechanism is still far from solved. I should like to read to you very briefly the remarks of Dr. B. F. Smith, a retired pathologist from Lancaster, England. He is recalling several cases he had seen in his earlier practice and thinks they represent "the psychic stress acting upon the magic circle of the endocrines, producing a materialistic disorder."

DR. HARRY A. OBERHELMAN Jr., Chicago: I would like to thank Dr. Ellison for his remarks. We have been unable to confirm the origin of these tumors from the alpha cells of the pancreas. We have used special stains, and in none of the cases that we have encountered can we say that the tumors are of alpha-cell origin.

The other point I should like to stress is careful examination of the duodenum, since we have had several cases in which the tumor has arisen in the wall of the duodenum. Recently exploration was done on a patient 70 years of age with steatorrhea of 15 years' duration, and a small nodule in the wall of the duodenum was the only finding. Examination of this nodule revealed a non-insulin-producing islet-cell tumor of the pancreas.

# Experimental Study of Interstitial Injection of Trypsin and Trypsinogen into the Pancreas

LUTHER M. KEITH Jr., M.D.; JAMES E. BARNES, M.D., and FRED R. DENKEWALTER, M.D., Columbus, Ohio

Many of the factors in the pathogenesis and experimental production of acute pancreatitis are conflicting and controversial. It is generally conceded that interstitially extravasated, active trypsin in the pancreas plays a dominant role.[1,2] Evidence further indicates that if, in addition, ductal obstruction or ischemia supervenes, necrotic or hemorrhagic pancreatitis is likely to ensue.[1-4] The pivotal issues seem to be (1) the mechanism by which trypsin or trypsinogen is extravasated, (2) whether trypsinogen itself can cause pancreatitis, and (3) the manner in which trypsinogen is activated.

The majority of investigators have utilized ductal perfusion of bile or pancreatic juice.[1,3] Stein and co-workers have produced hemorrhagic pancreatitis by injection of trypsin into the dog's pancreaticoduodenal artery and ligation of the pancreatic ducts. Hosie and Ziffren[5] have implicated collagenase, normally contained in pancreatic juice, as the initiator of pancreatitis. Since much of the experimental evidence indicating active trypsin as a dominant factor has been indirect, the effect of direct interstitial pancreatic injection of trypsin and trypsinogen was studied.

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From the Department of Surgery and the Surgical Laboratories, Ohio State University College of Medicine and University Hospital. Aided in part by a grant from the Comly Fund.

## Methods

Adult, fasting mongrel dogs were selected; blood for control serum amylase determinations was drawn, and the animals were anesthetized with intravenous pentobarbital sodium. The duodenum and pancreas were delivered through a midline incision. Four types of experimental conditions were established: 1. Trypsin, trypsinogen, or activated trypsinogen, 15 mg. per kilogram of body weight, was dissolved, diluted to 6 cc., and injected directly into the midportion of the left limb of the pancreas, and the site was marked with silk sutures (Fig. 1). 2. A 2-cm.-wide area of the pancreas in the same location was crushed, avoiding the pancreatic duct, and trypsin was injected as above (Fig. 2). 3. Five to six centimeters of the tail of the pancreas was meticulously mobilized from the splenic pedicle. Trypsin was injected into this segment, and it was placed in the retroperitoneal

Fig. 1.—Method and results of intrapancreatic injection of 15 mg. of trypsin per kilogram of weight in six dogs.

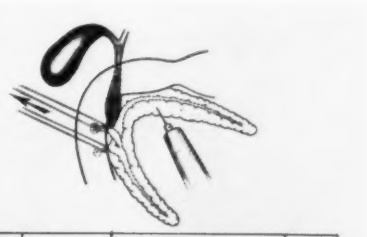
| NUMBER DOGS | Serum Amylase >500%† | Serum Amylase <500%† | Course: Benign | Course: Sick | Course: Expired | Course: Sacrificed | Autopsy |
|---|---|---|---|---|---|---|---|
| 6 | 5 | | 1 | 5 | 3 | 1 | +3 |

Fig. 2.—Technique and results of injection of 15 mg. of trypsin per kilogram at site of localized pancreatic trauma in three animals.

| NUMBER DOGS | Serum Amylase >500%† | Serum Amylase <500%† | Course: Benign | Course: Sick | Course: Expired | Course: Sacrificed | Autopsy |
|---|---|---|---|---|---|---|---|
| 3 | 2 | 1 | | 3 | 3 | | +3 |

| NUMBER DOGS | Serum Amylase >50%↑ | Serum Amylase <50%↑ | Course: Benign | Course: Sick | Course: Expired | Course: Sacrificed | Autopsy |
|---|---|---|---|---|---|---|---|
| 4 | 3 | | | 4 | 3 | | + 3 |

Fig. 3.—Method and results of injection of 15 mg. of trypsin per kilogram into mobilized tail of pancreas that was placed in the retroperitoneal space in four dogs.



| NUMBER DOGS | Serum Amylase >50%↑ | Serum Amylase <50%↑ | Course: Benign | Course: Sick | Course: Expired | Course: Sacrificed | Autopsy |
|---|---|---|---|---|---|---|---|
| 3 | 3 | | | 3 | 3 | | + 3 |

Fig. 4.—Technique and results of ductal obstruction and pancreatic injection of 15 mg. of trypsin per kilogram in three animals.

space through a transverse incision in the posterior parietal peritoneum medial to the upper pole of the left kidney (Fig. 3). 4. Both pancreatic ducts were identified through a duodenotomy by insertion of a probe. The ducts were then encircled by fine polyethylene tubes, containing stainless-steel wire, adjacent to the duodenum. These were tied over a subcutaneous button to obstruct the ducts, as described by Waite.[9] The duodenotomy was closed, and trypsin was injected into the left limb of the pancreas as before (Fig. 4).

The animals were allowed only water on the first postoperative day but subsequently were offered a standard kennel ration. They received no specific treatment for pancreatitis. Blood samples were obtained daily for amylase determinations, and their clinical course was observed. Dogs that died and those killed were autopsied.

## Results

*Trypsin.*—Sixteen animals were subjected to interstitial pancreatic injection of 15 mg. of trypsin per kilogram of body weight under four separate conditions.

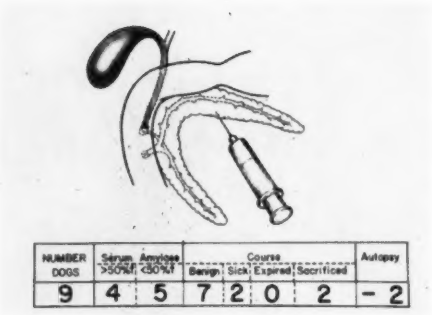
Six received trypsin injection without further manipulations (Fig. 1). Five dogs developed acute pancreatitis and had a stormy clinical course, and three died one to four days postoperatively. One animal was killed two days after injection. Necropsy demonstrated pancreatitis, varying from acute edematous to hemorrhagic in all four animals. The sixth dog had a benign course but, like the other five, had an elevated serum amylase.

The pancreas was crushed, avoiding the duct, at the site of trypsin injection in three animals. All three had a fulminating course of pancreatitis, elevation of serum amylase, and autopsy confirmation of hemorrhagic pancreatitis (Fig. 2).

The mobilized tail of the left limb of the pancreas was injected with trypsin and sutured within the retroperitoneal space of four dogs (Fig. 3). This was an attempt to produce pancreatitis anatomically analogous to human pancreatitis and to determine whether a pseudocyst would develop. All four animals became sick; three had a fulminating course, died, and had autopsy confirmation of severe pancreatitis. Three had elevated serum amylase values, but the fourth succumbed to pancreatitis before blood was obtained. Thus, the animals did not survive long enough for pseudocyst development to be determined.

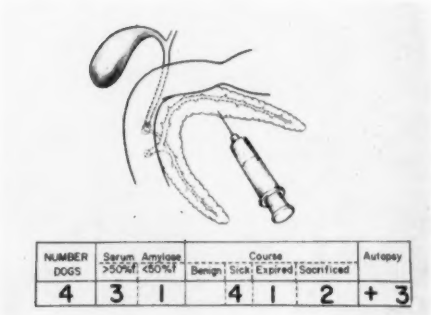
The pancreatic ducts were obstructed just before trypsin injection in three dogs. All three animals exhibited a fulminating course, died within five days, and were found to have hemorrhagic or necrotic pancreatitis at necropsy and elevated serum amylase levels (Fig. 4).

*Trypsinogen.*—Nine animals were subjected to interstitial injection of trypsinogen (Fig. 5). The first four dogs so injected had serum amylase elevations, and two of these were sick but survived. The trypsinogen received by these animals, however, was subsequently demonstrated to have proteolytic activity in vitro. Thus, basically



| NUMBER DOGS | Serum Amylase >50%↑ | Serum Amylase <50%↑ | Course Benign | Course Sick | Course Expired | Course Sacrificed | Autopsy |
|---|---|---|---|---|---|---|---|
| 9 | 4 | 5 | 7 | 2 | 0 | 2 | − 2 |

Fig. 5.—Method and results of injection of 15 mg. of trypsinogen per kilogram into the pancreas in nine dogs. Trypsinogen injected in the four animals with elevation of serum amylase was found to have proteolytic activity.



| NUMBER DOGS | Serum Amylase >50%↑ | Serum Amylase <50%↑ | Course Benign | Course Sick | Course Expired | Course Sacrificed | Autopsy |
|---|---|---|---|---|---|---|---|
| 4 | 3 | 1 | | 4 | 1 | 2 | + 3 |

Fig. 6.—Method and results of injection of 15 mg. of activated trypsinogen per kilogram into the pancreas of four animals.

these animals were analogous to the dogs injected with trypsin.

The remaining five dogs had no significant rise in amylase after trypsinogen injection and exhibited a benign course. The trypsinogen they received was of a different lot from that used in the first four dogs and was proved to have no proteolytic activity. Two animals were killed two days after injection and had only minimal edema at the site of injection.

*Activated Trypsinogen.*—Four dogs received similar injections of proved inactive trypsinogen which had been activated (Fig 6). In contrast to those injected with inactive trypsinogen, these animals were all sick and had elevations of serum amylase. One died, and two were killed two days after injection. Necropsy confirmed severe pancreatitis in the last three dogs.

## Comment

The capability of interstitially extravasated, active trypsin to produce acute pancreatitis was demonstrated. Direct injection into the pancreas afforded a source of interstitial trypsin with minimal mechanical damage to the ductal system, in contrast to forceful ductal perfusion. The severity of the resultant pancreatitis and its incident mortality were increased by the addition of trauma, ductal obstruction, or placing the injected segment of pancreas in the retroperitoneal space. The increased severity of pancreatitis in the last instance may be related to operative trauma, to alteration in blood supply by mobilization, or to greater susceptibility of the retroperitoneal space to the resultant extravasation.

In contrast to these results of trypsin injection, no such capacity of inactive

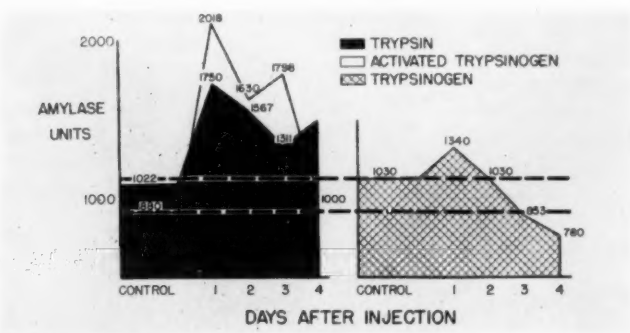



Fig. 7.—Comparative graphic representation of composite average serum amylase values in all animals before and four days after interstitial injection of trypsin, trypsinogen, and activated trypsinogen. The heavy horizontal dotted lines indicate the range of control values. Consistent elevations were found after injection of both trypsin and activated trypsinogen, but only minimal transient increases occurred after trypsinogen injection.

trypsinogen to produce significant pancreatitis was demonstrated (Fig. 7). This may be due to the presence of a "trypsin inhibitor," as described by Kunitz and Northrop.[7] These results suggest that the inhibitor is able to cope with the small amounts of trypsin resulting from intrapancreatic activation of trypsinogen but not with large amounts of active trypsin.

The trypsinogen utilized in this experiment was shown to be capable of activation and, when activated, to produce pancreatitis on interstitial injection.

This study indicates that there is little or no activation of extravasated trypsinogen within the normal dog's pancreas, challenges the capability of inactive trypsinogen per se to produce acute pancreatitis, emphasizes the role of active trypsin in the pathogenesis of pancreatitis, and, finally, suggests that trypsin inhibition may be a significant factor in preventing or limiting the severity of acute pancreatitis.

## Conclusions

Interstitial pancreatic injection of trypsin produces acute pancreatitis. The severity and mortality of resultant pancreatitis are increased by ductal obstruction or trauma.

Interstitial pancreatic injection of trypsinogen (1) failed to produce pancreatitis and (2) *did* produce pancreatitis when activated.

Department of Surgery, Ohio State University College of Medicine.

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## DISCUSSION

DR. EDWARD E. MASON, Iowa City: I am substituting for Dr. Ziffren, who was unable to attend this meeting but who has been interested in this problem.

Pancreatitis seems to be difficult to understand clinically and experimentally. It is like a sword of Damocles or a large boulder on a slightly inclined plane. What gets it started, and how far does it go? There is no doubt that in injury, trypsin can start the process off, as was demonstrated in this work.

The small amount of trypsin released from trypsinogen which was injected is not enough to start the process. What, then, forces this trypsinogen under certain circumstances to become activated, and for the process to go on to the extent of causing actual damage to blood vessel walls and hemorrhagic pancreatitis?

Dr. Ziffren has found collagenase in the pancreatic juice and feels that in certain instances this may be the additional enzymatic process which injures blood vessel walls and starts the process toward hemorrhagic pancreatitis.

In 1936, Rich and Duff, in their classical monograph, described injuries to the media of blood vessel walls after the injection of pancreatic juice subcutaneously. I would like to ask Dr. Keith whether he and his co-workers noticed similar changes in the blood vessel walls after these experiments.

I would also like to ask whether an attempt was made through heating the trypsin to determine whether or not this was trypsin, or whether collagenase was perhaps present in the material they injected.

DR. LUTHER M. KEITH, Jr., Columbus, Ohio: I appreciate Dr. Mason's remarks and Dr. Ziffren's communication through him.

In answer to the two questions, we were unable to demonstrate very great change in the vessels within the pancreas. The most devastating damage

we saw was in the interstitial or areolar fibrous tissue of the pancreas, which was often necrotic and hemorrhagic.

I had anticipated that Dr. Ziffren, and possibly Dr. Mason, might be interested in the aspect of whether or not in fact this trypsin or trypsinogen contained collagenase, but I am sorry to say the work has not gone far enough so that we were able to heat the trypsin or trypsinogen, as they have suggested, to inactivate any possible collagenase contained therein.

If I may project the significance of this study, it indicates that there is little or no activation of trypsinogen within the normal dog's pancreas. It challenges the capability of trypsinogen itself to produce acute pancreatitis, and again emphasizes the role of active trypsin in the pathogenesis of pancreatitis.

# Chyloperitoneum

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Few clinicians have the opportunity in a lifetime of practice to observe a case of massive chyloperitoneal effusion. This is evidenced by the multiplicity of single case reports, with few exceptions.[2,12,41-43] Chylous ascites is a manifestation and not a disease entity; it represents an "obstructive phenomenon." Although the etiology is unknown, there is usually some distinct pathologic condition appearing simultaneously in the patient to account for the effusion. An abnormal accumulation of chyle occurs in the pleural, pericardial, and peritoneal cavities and is seldom diagnosed preoperatively in the last two sites. The purpose of this paper is to review some of the data pertaining to the lymphatic system and to report three cases of chylous ascites recently encountered.

Since Aselli discovered the lymphatic system in 1622, considerable information has been brought forth relative to the properties and function of lymph. Bartholin, in 1651, described the first case of chylothorax. Twenty-two years later Duverney (1683) attempted ligation of the thoracic duct. Flandrin (1691), a veterinarian, successfully ligated the thoracic duct in the neck of a horse and cannulated it to study the properties of lymph. In 1694, Morton described the initial case of chylous ascites in a 2-year-old boy as follows:

> But at the very beginning of the Fever his belly began to be distended with a dropsical swelling, which increased strongly every day; his Cough and shortness of Breath at the same time growing worse; All of which symptoms were at length accompanied with an Atrophy of the Parts, even to the degree of a Marasmus. But yet when his body was a perfect Skeleton, and the Dropsie at a high Tide (which was very remarkable) he had a brisk and healthful look, and a lovely countenance, without the least Tincture of a yellowness, and a good, or rather greedy Appetite, and that to the very day he died. From whence I did rightly conjecture, and always told his Friends, as my opinion, that his Dropsie was truly chylous, caused by the chyle flowing into the cavity of the Belly by lacteal vessels upon some rupture that had been made in them; which appeared very plainly from the Event.[30]

It was not until 1892 that Bargebuhr described chylous accumulations in the pericardial cavity.

## Lymphatic System

The cisterna chyli and thoracic duct pursue a long and tortuous course, in close relationship to many structures. Both structures are vulnerable to occlusion from external pressure of various types. The thoracic duct is 38-45 cm. in length and begins at the level of the first of second lumbar vertebra as an elongated, triangular dilatation by receiving the right and left lumbar lymphatic and the unpaired intestinal trunks. From the cisterna, the duct runs superiorly along the right side of the aorta, picking up the efferent lymphatic channels from the lower six intercostal trunks. It traverses the diaphragm via the aortic hiatus, and thus the cisterna chyli becomes the thoracic duct and ascends in the posterior mediastinum, between the azygous vein and the aorta. At the level of the fifth thoracic vertebra, the duct crosses the midline to the left and enters the superior mediastinum. Here it ascends behind the aortic arch to the root of the neck, between the esophagus and the left mediastinal pleura. The arch formed by the thoracic duct at this level rises approximately 3 cm. above the

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clavicle and empties into the left innominate, left subclavian, or left internal jugular vein. The only competent valve in this system is located at its termination into the venous system. Cephalad to the diaphragm, before emptying its contents into the venous system, the thoracic duct receives the left jugular, left subclavian, and left bronchomediastinal trunks, as well as efferents from the posterior mediastinum, the lateral intercostal lymph nodes of the upper left six spaces, and the upper abdominal lymph nodes, which pierce the crus of the diaphragm. The thoracic duct transports lymph from all parts of the body except the right side of the head, neck, thorax, and right superior extremity, which are drained by tributaries of the right lymphatic duct. The latter is approximately 1.25 cm. in length, courses along the medial border of the scalenus anterior to the root of the neck, and ends in the right subclavian vein at its juncture with the right internal jugular vein.

Lymph clots very slowly (owing to low fibrinogen concentration) and is sterile on culture. Lymph has a milky appearance, stains positive with Sudan III, and is alkaline in reaction. Large numbers of lymphocytes are present. It functions to remove colloidal material from the tissues. The composition varies with digestion, since the amount of lipid content varies directly with the quantity of fat in the diet. Chyle circulates toward the heart at the rate of 1.0 to 1.5 ml. per minute. The rate of flow is influenced (1) by the positive intra-abdominal and negative intrathoracic pressure and (2) by the contraction and relaxation of the smooth muscle fibers in the wall of the thoracic duct, controlled by parasympathetic and sympathetic stimulation, respectively. The pressure in the thoracic duct is −9.5 mm. Hg or less in the larger trunks; this pressure is exaggerated during inspiration. Lymphatics do not occur in the central nervous system, bone, inner ear, pulmonary alveoli, splenic pulp, eyeball tunics, or fetal placenta. Lymphatics resemble veins in their structure but are thinner than veins of corresponding caliber.

## Etiology

A review of the literature reveals that mechanical obstruction of the thoracic duct or cisterna chyli is the common factor in the pathogenesis of chyloperitoneal effusions. Numerous cases have been reported, however, in which no obstruction was found, either at surgical exploration or post mortem.[2,17,19,25,32,39,42] Occlusion causes the pressure within the duct to rise to high levels, with subsequent damming back of chyle. Palken and Weller[35] have observed that a high thoracic duct pressure may exist without evidence of chylous ascites. Chylous ascites has been reported to be associated with intra-abdominal, retroperitoneal, thoracic, and mediastinal neoplasms[8,22,30,32,35]; others have observed it secondary to trauma,[8,28,29] mesenteric adenitis,[12,16,29] the acute abdomen,[7,19,20,21,24,35,37,41] syphilis,[21] tuberculosis,[6,28] congenital defects of the lymphatic system,[16,43] pregnancy,[19] embolic occlusion of the left subclavian vein,[35] nephritis,[2] leukemia,[10] adhesive bands,[11,44] midgut volvulus,[44] filariasis (duct obstructed by parent worm)[41] and bilharziasis (duct obstructed by blood fluke),[41] and thoracic-duct blockage by aneurysm.

Lynch,[30] is discussing the work of Wallis and Scholberg, stated that of the 171 cases reported by them in a collective review covering the period from 1860 to 1910, malignant abdominal neoplasms was the cause in 81. Norment[33] did an exploration on a 64-year-old woman with a carcinoma of the stomach which was freely movable and operable but not resectable, owing to the large amount of chyle present. Jackson,[22] in exploring a large, nonresectable retroperitoneal mass (lymphoblastoma), found dilated, ruptured lacteals, due to pressure from the large tumor. Post mortem, tumor tissues may be found completely occluding the lumen of the thoracic duct.[18] The role of mesenteric adenitis is uncertain in the pathogenesis of the chylous abdomen.

Davis [12] observed that some relationship exists between chylous ascites and mesenteric adenitis, the adenitis being possibly of tuberculous origin. Kuykendall,[27] while performing a right inguinal herniorrhaphy, discovered a chylocele; later a laparotomy was performed (for abdominal distention), and 400 ml. of chyle was found, in addition to the presence of numerous large lymph nodes in the mesentery. Gribetz,[16] in 1951, reviewed 25 cases of chylous ascites in infants and found 4 instances in which mesenteric adenitis was the only pathologic finding and perhaps represented the obstructing lesion. Hoffman,[20] in an excellent review of chyle peritonitis complicating the acute abdomen, discussed the pathogenesis and reported an additional case. Laparotomy was performed in all cases with a preoperative diagnosis of perforated ulcer, acute cholecystitis, acute appendicitis, strangulated hernia, abdominal trauma, small-bowell obstruction, or mesenteric thrombosis, with only two deaths recorded. Hoffman concluded "that chyle outside its own retaining vessels is a noxious substance which can produce peritoneal irritation mimicking exactly or otherwise inflamed peritoneum." Gribetz, in discussing this syndrome in infants and children, was of the opinion that these effusions may be due (1) to a congenital weakness of the lymphatic channels, allowing the escape of chyle, or (2) to a congenital defect of the larger lymphatics, causing a blockage which produces dilation of the smaller lymphatics, due to back-pressure. Young and Lee [43] found chylous ascites in siblings 25 months of age and wrote that the coincidence in siblings at an early age speaks for an anomaly of the lymphatic system. In infants the system is so delicate that at autopsy or during a surgical procedure the duct is difficult to find and injection of the structure is seldom satisfactory.

Accumulations of free chyle in the peritoneal cavity have an irritating effect on the gastrointestinal tract, and oftentimes patients present themselves with an intractable diarrhea or anemia (Case 2). At operation or autopsy the lacteals are markedly dilated and the mesentery and serosa are engorged. Large mesenteric, paravertebral, and retroperitoneal nodes are encountered. The abdominal organs at times have a milky-white appearance due to subserosal collection [5] of lymph. Small bowel and, less often, large bowel may be involved, being thick, dilated, edematous, and hyperemic. Occasionally this is confined to a segment of small bowel, as in our Case 1, and as with others.[12,25,41] In our case we have been unable to correlate the chyloperitoneal accumulation with the proximity of the pathologic segment of jejunum to the ligament of Treitz. Frequently, and particularly in infants and children,[16] there may be a chylocele (lymphocele) present[16,26,41]; this is attributed to the partially open condition of the tunica vaginalis. This was also evident in our Case 1.

## Experimental Production

Although chylothorax has been reproduced experimentally in animals, attempts to produce chyloperitoneum have met with failure. Sir Astley Cooper, in 1798, ligated the thoracic duct in dogs and reported that the cisterna had burst, with extravasation. Magendie (1821) reported on the results of Dupuytren, who ligated the thoracic duct in the neck of horses, and he stated that death resulted only when the duct was completely ligated. Leuret and Lassaigne, in 1825, ligated the thoracic duct in the neck of dogs and reasoned that chyle took an abnormal course to enter the blood stream, probably via the portal vein; they later ligated the portal vein and found blood in the cisterna.

Wutzer (1834) demonstrated three communications between the duct and the azygos vein in a 37-year-old woman. In 1873 Colin concluded that ligation of the thoracic duct did not always give the same results, owing to the variable emptying of the duct into the venous system, and that, therefore, it was probably impossible to prevent lymph from entering the blood stream. Schmidt and

Muhlheim (1877), in their experiments, planned to determine whether or not the products of albumin reached the blood stream via the thoracic duct. The external and internal jugular, axillary, and innominate veins, right and left, were ligated at the base of the neck in dogs. To prove that occlusion was complete, Berlin (Prussian) blue was injected into the cisterna at a pressure of 40-50 mm. Hg in the postmortem subject. They found a complete obstruction and also observed that digestion and absorption of albumin, as well as the conversion into urinary products, were the same as when chyle outflow was not obstructed. Boegehold (1883) was interested in wounds of the thoracic duct and noted that the integrity of the thoracic duct was not essential to life, and he presented clinical cases to substantiate this premise.

Cushing (1898) was of the opinion that when the thoracic duct was ligated the lymph current would be reversed and, finally, that all lymph would be routed through the right lymphatic duct. Lucibelli (1902) ligated the thoracic duct in large dogs and gave them milk four to five hours before laparotomy. Lucibelli postulated that complete obstruction of the duct caused death and that partial ligation caused little disturbance because collateral lymphatics become established early. Complete ligation caused changes in all the organs, and Lucibelli attributed the histological changes to the toxicity of stagnant lymph.

Munk and Friedenthal (1901) observed fat to be increased in the portal vein after ligation of the duct and the per cent of fat in the portal vein to be higher than that in the jugular vein. Silvester (1912) described permanent connections between the lymphatic and the venous system at the level of the renal veins in South American adult monkeys. Job (1915) reported similar communications with the inferior cava, iliolumbar, renal, and portal veins in rats.

### Classification of Chylous Effusion

Obviously, all cloudy or milky fluids aspirated from the pleural or peritoneal cavities are not chyle. Numerous attempts have been made to classify these effusions, with minimal success. Quincke[33] classified them as follows: (1) hydrops chylosus: all chyle effusions into serous cavities in which there is direct anatomical evidence pointing to the lacteals and general lymphatic system; (2) hydrops adiposus: when the presence of fat is due to degenerative products, and not to an addition of chyle, and (3) pseudochylous ascites: milky fluid caused by substances other than fat.

Blankenhorn[2] similarly separated these fluids into three groups: (1) those effusions due to obstruction of lacteals or thoracic duct which can be demonstrated and fluid proved to be chyle; (2) the effusions due to degenerating tumors or cysts which discharge cholesterol into a cavity filled with serum, and (3) the effusions due to chronic diseases of the liver, kidney, or peritoneum (fluid not chyle).

Ferrara and Walker[13] sought to simplify this classification into two groups only: (1) the fluid which is true chyle, and (2) pseudochylous effusion due to the presence of lecithin and globulin in finely divided suspension, resulting from degeneration of cellular elements. They identified true chyle by placing 5 ml. of the fluid obtained in a test tube and, after adding a few drops of ether, shaking the mixture. The ether with the extracted fat floats on top, leaving a clear fluid below this layer.

Strauss[20] sought to identify true chyle by altering the fat content in the diet and correlating corresponding changes (by analysis) with fluid obtained from abdominal paracentesis. Kessel[25] obtained 104 oz. (3.12 liters) of chylous fluid from the abdomen of an 11-week-old infant (on four paracenteses) and, in analyzing this fluid, found that the total solids, protein, and fat values were in the same proportion as those of human milk (or that milk which the patient was being fed), but that the ash, calcium, and chloride values were outside the recognized limits of breast milk. Lactose, a

TABLE 1.—*Classification of Chylous Effusions* *

I. True chylous effusion

1. Milky appearance
2. Separates into a creamy layer on standing
3. Odorless or has the odor of ingested food
4. Specific gravity over 1.012
5. Total solids over 4%
6. Fat content high (0.4% to 4.0%)
7. Alkaline reaction
8. Total protein over 3%
9. Sterile and resists putrefaction
10. Fat globules stain with Sudan III

II. Chyliform (due to fatty degeneration of cells)

1. Specific gravity over 1.012
2. Fat solids less than 2%
3. Total protein less than 3%
4. Low fat content

III. Pseudochylous effusion (appearance due to pus)

* After Johsman.[23]

normal constituent of breast milk, was absent from chyle.

Jahsman,[23] in classifying chyloperitoneal effusions, recognized three groups (true chylous, chyliform, and pseudochylous), with definite criteria for each grouping. This classification seems most acceptable, since he has adroitly utilized the chemical and physical properties of lymph to categorize these effusions (Table 1).

## Diagnosis

Chyloperitoneum is rarely diagnosed preoperatively, and in this regard we were fortunate in the three cases. Paracentesis should be performed in all cases of ascites. Wyatt and Gross [42] obtained a scout film of the abdomen in a 6-day-old infant and observed the following:

> The liver is clearly delineated as a smooth radiopaque structure surrounded by fluid which was relatively translucent. The contrast between the density of the liver shadow and that of the surrounding fluid was the only feature which differed from the usual appearance of ascites.

Commenting further, Wyatt and gross stated that fat has increased radiolucency as compared with soft tissues of the body; other tissues with a high lipid content also have this property. Levering [28] was also able to demonstrate these roentgen findings in his case, whereas other authors [16,42] have been unable to do so.

Blood and Fairchild [3] administered 5 gm. of Sudan III in butter to a 12-month-old infant, and they were able to obtain pink-tinged chyle from the peritoneal and pleural cavities. Evans blue (T-1824) has been recommended for use in outlining the thoracic duct.[15] If a 1% solution of Evans blue is used intravenously, the dye appears in 1 hour and the staining lasts 1 hour 10 minutes; if administered subcutaneously, the dye appears in 2.3 minutes and the duct remains stained for 12 minutes. Klepser and Berry [26] favor the use of lipophilic dyes because they are safe, cheap, simple, fat-soluble, and nontoxic. These dyes are D&C Red No. 17 [1-*p*-phenylazophenylazo-2-naphthol], D&C Red No. 18 [1-xylylazo-xylxylazo-2-naphthol], and D&C Green No. 6 [quinizaringreen SS; 1,4-bis(*p*-toluino)-anthraquinone], approved by the Food and Drug Administration, and may be given in a sandwich or by Levine tube with olive oil. Sky blue [aqueous solution of the sodium salt of 3,3-dimethoxydiphenyl-4,4-diazo-bis (8-amino-1-naphthol-5,7-disulfonic acid)] usage is intended for the visualization of lymph nodes and is presently in use in resection for gastric, intestinal, bronchogenic, or pelvis carcinoma.

## Report of Cases

CASE 1.—A., a 66-year-old man, referred by Dr. Arthur Abts, Omaha, was initially seen in October, 1948, at St. Joseph's Hospital with a nonproductive cough and sinusitis of three or four years' duration. There has also been an associated 20 lb. weight loss during the six months preceding hospitalization. Two months previous to admission, he had had a bout of penumonia. On admission, except for a few moist rales in the base of the right lung, there were no significant physical findings. RBC 3,950,000; hemoglobin 12 gm. per 100 cc. (78%); WBC 9250, with a normal differential count. Urinalysis was negative. On Oct. 2, bronchoscopy was performed. The right main bronchus was filled with purulent exudate. Fluid obtained from bronchoscopy showed no growth on culture, as was true of the fluid obtained from a previous thoracentesis. No acid-fast bacilli were seen on direct smear, and guinea-pig inoculation was nega-

tive on examination on Nov. 26. On Oct. 5 a nasal antrostomy for right suppurative maxillary sinusitis was performed. On Oct. 27 a right thoracic decortication was performed for a "trapped lung," with uneventful recovery.

This patient was seen again seven years later, at which time he had exertional dyspnea and dependent and scrotal edema, with an enlarged abdomen. On examination, the abdomen was obviously distended; the presence of dependent and scrotal edema was also noted. Respirations were labored. Numerous rales were audible throughout both lung fields on auscultation. A soft, blowing, nonradiating systolic murmur was heard at the apex of the heart. Blood pressure 124/52. A fluid wave could be elicited in the abdomen, and shifting dullness was also present. A caput medusae was evident. There was marked edema of the legs and scrotum. Other findings included a reducible right inguinal hernia, external hemorrhoids, fullness in the rectal shelf, and numerous superficial varicosites on both lower limbs. RBC 4,260,000; hemoglobin 13.1 gm. per 100 cc. (85%); WBC 4650, with a normal differential count. Urinalysis was normal. Serology negative. NPN 31.2 mg. %; prothrombin time 12 seconds (100%); serum proteins 5.85 gm. % (albumin 3.9 gm. %, globulin 1.95 gm. %). Direct bilirubin 0.00 mg. %; indirect bilirubin 0.45 mg. %; sulfobromophthalein (BSP) 9.25% in 30 minutes. Abdominal fluid: positive for fat; specific gravity 1.016, negative for acid-fast bacilli. No acid-fast bacilli seen on smear of fluid obtained by thoracentesis. Circulation time 14 seconds, arm to tongue (dehydrocholic acid U. S. P. [Decholin]). On June 17, 1955, an abdominal paracentesis was performed, and 1500 cc. of yellow, milky fluid was obtained. On June 18, thoracentesis was negative in the right pleural cavity, and 400 cc. of cloudy, gray fluid was obtained from the left chest. Reexamination of the fluid from the abdomen on June 19 showed no malignant cells, was sterile on culture and negative on guinea-pig inoculation, and stained with Sudan III. Laparotomy on July 6 failed to reveal the point of obstruction of the cisterna chyli or thoracic duct. Analysis of abdominal fluid obtained at surgery gave findings listed in Table 2.

The patient was readmitted Oct. 9, 1955, with a left chylothorax, chylous ascites, scrotal edema, marked anemia (2,600,000 RBC), and a marked hypoproteinemia. D&C Green No. 6 was administered by Levine tube, and reexploration was undertaken on Oct. 19, at which time a 3 ft. segment of jejunum close to the ligament of Treitz was found which was thick, edematous, and hyperemic, with numerous dilated, green lacteals. This segment of small bowel was resected, with a side-to-side anastomosis. Postoperatively, the patient received 19 units of whole blood and 2 units of serum albumin. No recurrence of the chyloperitoneum followed the above procedure.

TABLE 2.—*Analysis of Fluid from Patient A*

| | |
|---|---|
| Total protein | 2.61 gm. % |
| Albumin | 1.54 gm. % |
| Globulin | 1.07 gm. % |
| A/G ratio 1:0.42 | |
| Total cholesterol | 169.38 mg. % |
| Free cholesterol | 97.05 mg. % |
| Esterified cholesterol | 72.33 mg. % |
| Lipid phosphorus | Negative |
| Total fat | 2721.93 mg. % |
| Fatty acid | 111.43 mM/L. (308.8 mg. %) |
| Neutral fat | 2413.13 mg. % |

CASE 2.—Mrs. B., referred by Dr. Russell R. Williams, was admitted to St. Joseph's Hospital, Feb. 12, 1956, complaining of progressive abdominal fullness of two months' duration, with weakness, lassitude, an 11 lb. weight loss, nausea, vomiting, and diarrhea. During the three weeks prior to admission, she had progressive exertional dyspnea and a nonproductive cough, with progressive enlargement of the abdomen. In 1944 a benign tumor was removed from the left breast. In 1948 the patient had an appendectomy, with uneventful recovery.

On physical examination her blood pressure was 150/80. The abdomen was markedly distended, and a fluid wave could be elicited. There was 2+ tenderness in the right upper quadrant. A mass was present in the left side of the abdomen, well outlined, 8×10 cm. in diameter, smooth, not movable, and nontender. There was a healed McBurney incision. Pelvic examination revealed that the uterus was uniform in size and freely movable; there was a left adnexal mass continuous with the uterus, measuring 3×4×2 cm. Previous Papanicolaou stains of the cervix were reported as Grade 2.

RBC 4,860,000; hemoglobin 13.5 gm. per 100 cc. (88%); WBC 8330, with 73 segmented forms, 2 band forms, 2 eosinophils, 2 basophils, and 21 lymphocytes. Serology negative. Urinalysis normal. Prothrombin time 14.5 seconds (65%). Sulfobromophthalein retention 19.75%. Fasting blood sugar 104 mg. %; serum proteins 5.79 gm. % (albumin 4.45 gm. %, globulin 1.34 gm. %). Analysis of fluid obtained from abdominal paracentesis showed total serum protein of 5 gm. %, no growth on culture, and no acid-fast bacilli. Fluid obtained from left paracentesis showed no growth on culture, a negative stain for acid-fast bacilli, 80% monocytes, and 20% polymorphonuclear cells. Tuberculin skin test (purified protein derivative of tuberculin U. S. P., first strength) was negative at 48 hours.

On Feb. 22, 1956, laparotomy was performed; a large retroperitoneal mass, extending from the

sacral promontory to the diaphragm on the left side of the abdomen, was obviously inoperable. There were extensive intra-abdominal metastasis, and approximately 200 cc. of chyle was present. Biopsy of the mass showed it to be a malignant lymphoma. After surgery, the patient began an extensive course of external irradiation.

CASE 3.—Mrs. C., referred by Dr. A. J. Schwedhelm, Norfolk, Neb., was admitted with a history of increasing dyspnea and enlarging abdomen of several weeks' duration. A preoperative diagnosis of chylothorax and chyloperitoneum was made. Thoracentesis was performed to empty both pleural cavities. Laparotomy was performed on May 20, 1957, and a huge, inoperable retroperitoneal lymphoma was found.

Postoperative x-ray therapy was instituted immediately after the laparotomy. There has been no evidence of recurrence of chylothorax as long as eight months postoperatively.

## Comment

The chief reason for including Cases 2 and 3 is to furnish contrast to Case 1. Cases 2 and 3 represent the relatively common type of "secondary chyloperitoneum." There is nothing unusual to discuss relative to these cases except to point out the importance of diagnostic paracentesis, and the need for exploratory laparotomy in all cases of chyloperitoneum and for careful evaluation of therapeutic measures. Spontaneous "cures" following various surgical procedures are common.

Case 1 more nearly approximates a new entity, not previously described. The interesting, unexplained pleural effusions seven years prior to the appearance of the ascites may or may not have etiological significance. Incidentally, the efficiency of the decortication and fusion of the lung peripherally is evidenced by the fact that no accumulation of chyle was possible in the corresponding hemithorax. The filtration power of the lymphatics of the diaphragm was also of note, since the great difference in concentration of the chyle removed from the peritoneal cavity and that from the hemithorax was most evident. This has also been noted in other "transudates" secondary to the presence of various fluids within the peritoneal cavity (i. e., bile, pus). Spontaneous remission in the chyloperitoneum in Case 1 did not occur after the first laparotomy. The important therapeutic event was the subsidence of the ascitic effusion immediately following the removal of an unusual pathologic segment of jejunum with tremendously dilated lacteals. It is true that even a remission could follow a second operative procedure, but it would be unusual percentagewise, in view of failure of the first laparotomy to produce a remission, of the presence of the diseased jejunal lacteals, and of the absence of any other explanation for the chyloperitoneum. No recurrence of the chyloperitoneum has followed the laparotomy, and the patient remains well three years later.

It is felt that this may represent a true "primary chyloperitoneum," with complete cure following eradication of a diseased portion of jejunum.

## Treatment

The treatment of secondary chylous ascites varies with the type of obstruction to the flow of lymph to the venous system. In numerous instances no treatment was instituted or identified.[10,17,18,25,33,35,36] Providing a malignant lesion is not suspected, the treatment of choice is repeated—abdominal paracentesis combined with vigorous supportive therapy. In most instances laparotomy is necessary to rule out a malignancy.

In massive accumulation of chyle in the peritoneal cavity, a sustained effort must be directed toward replacing the great loss of protein (particularly albumin) and correcting the associated anemia. Serial blood counts and plasma protein determinations serve as a guide to replacement therapy. Frequent small blood transfusions are perhaps the happy medium when anemia and hypoproteinemia exist simultaneously. Care must be taken in transfusing patients with long-standing anemias to avoid overloading the heart and a contracted peripheral vascular bed.

These patients should be kept on a high-protein, high-carbohydrate, low-fat diet; the low concentration of lipids in the diet reduces the volume of chyle produced. Multivitamins are given, so that the patient receives a minimum of 500 mg. of ascorbic acid, 10,000 units of vitamin A, 50 mg. of thiamine hydrochloride, 10 mg. of riboflavin, 100 mg. of nicotinamide, 15 mg. of pyridoxine hydrochloride, and 25 mg. of pantothenic acid equivalent.[14] Protein hydrolysates may be employed because of the high protein content of these fluids. Most of these preparations contain 5% dextrose, so that protein is spared. Human albumin is effective and more rapid in correcting the protein deficiencies in the plasma.

The reintroduction of chyle into the circulation (by vein) has been reported. Little et al.,[29] in treating a 17-year-old girl with a traumatic chylothorax and chylous ascites, aspirated a total of 108,500 cc. of chyle from the peritoneal cavity and 22,385 cc. from the left pleural cavity during a four-month period of hospitalization. All chyle obtained from thoracentesis was returned to the patient intravenously in 29 separate transfusions (the largest being 1200 cc.), with only a single minor reaction. During the course of these transfusions, however, she developed some embarrassment of the circulation of the lower extremities, and the authors questioned whether or not chyle thrombosis occurred at the venous-lymphatic connections.

In 1944, Forbes[15] reintroduced chyle in a 6-week-old infant after failure of conservative therapy. Using sterile precautions, chyle was introduced directly from the thorax into flasks containing sodium citrate to make a final concentration of 0.25%. Small amounts were then injected subcutaneously and then into a vein, and the baby exhibited no reaction to the procedure. Chyle was then given in amounts varying from 60 to 100 cc. per transfusion, for a total of 14 times over a period of 38 days, without reaction. The fluid was always used in a period of 48 hours after withdrawal from the chest. In spite of maximum effort to correct her state of nutrition, she died. Forbes reported two deaths which occurred after use of chyle intravenously.

Attempts at surgical decompression of the abdomen following failure of conservative measures have been approached with varied procedures and dubious results. Simple drainage (Penrose, cigarette, Chaffin tube) combined with short-term dietary therapy has afforded recovery in several cases.[7,11,12,24,27,30,34] Venous-peritoneal shunt, saphenocutaneous shunt, and anastomosis of the renal pelvis to the peritoneal gutter are procedures that have been employed to clear chyle ascites. The operations have the advantage of avoiding repeated paracentesis, returning the patient's protein, and relieving ascites, and is actually a slow clysis. Huber and Silver (1914)[21] performed a laparotomy on an 8-year-old boy and elected to use silk to drain the abdomen bilaterally into the subcutaneous tissue of the thigh. They pointed out that Lambotte, of Antwerp, was the first to use silk to drain the abdomen, and Mr. W. Sampson Handley employed silk later as artificial lymphatics in cases of brawny edema of the breast, as well as for abdominal fluid.

Morse[32] recalled Routte's successful use of saphenoperitoneal shunt in two of three cases and therefore employed this procedure in a 42-year-old man with chyloperitoneum. Initially, the shunt was done on the right side, with no diminution of ascitic fluid. A left shunt was then performed, and there was no evidence of chylous effusion postoperatively. Wegner[40] described an infant of 5 months as a "toy balloon to which are attached a paper head and dangling paper arms and legs." In exploring this patient's peritoneal cavity, he was unable to locate the point of obstruction. At the second laparotomy, he successfully performed a venous-peritoneal shunt (using the saphenous vein), with no evidence of

recurrence of chyle as long as 14 months following surgery.

Button, in 1946,[6] reported the case of a 10-year-old girl who developed a traumatic chylous abdomen. Owing to the increasing frequency of paracentesis and generalized debilitation, a right venous-peritoneal shunt was performed, and the omentum was amputated to prevent obstruction of the shunt. This patient was free of chyle accumulation one year postoperatively.

Whittlesey et al.[41] discussed both saphenoperitoneal and saphenocutaneous shunts and commented that, although it is logical to return the chyle to the venous system, it is unreasonable to expect the shunts to remain patent for a prolonged period of time. In treating a 3-year-old male patient with three previous negative laparotomies for chylous ascites, they performed a fourth operation, consisting of a left saphenoperitoneal shunt, and in doing so utilized the hernial sac from an indirect left inguinal hernia. There was no evidence of recurrence after surgery.

Blood and Fairchild[3] reported a case of a 12-month-old male infant with recurrent abdominal distention and chylothorax. A left saphenoperitoneal shunt was performed, but the chylous ascites and chylothorax persisted. Two months later, a right saphenoperitoneal shunt was done, but there was continued accumulation of chyle in both chest and abdomen. The patient later experienced a spontaneous recovery.

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## DISCUSSION

DR. JACOB K. BERMAN, Indianapolis: When Dr. McCarthy asked me to discuss his very interesting paper, I told him that I was familiar with one phase of the subject which is only briefly mentioned in the literature, namely, chylous ascites in early nutritional cirrhosis. In all of my writings I have referred to atrophic, or Laennec's, cirrhosis, but the terminology and nomenclature of this condition need much clarification, and classifications are now more enlightening when based on etiology or on morphology. However, the cause of cirrhosis is not always apparent or known, and diagnoses on morphological changes alone leave much to be desired.

For example, nutritional cirrhosis is usually preceded by a fatty metamorphosis (fatty cirrhosis), which may be due to dietary deficiency or to deficiency in lipotropic factors; and in America this is usually associated with chronic alcoholism (alcoholic cirrhosis). The progress of this disease leads to what on morphological grounds has been termed portal, or Laennec's, cirrhosis. Hyaline changes in hepatic cells precede necroses more commonly in alcoholic cirrhosis (Mallory's alcoholic hyaline lesions), and fibrosis abounds particularly in the septa (septal cirrhosis), finally leading to a fibrous tissue content of roughly 25%, as against the normal 2% to 3%. Of course, the size of the liver is inversely proportional to the amount of scar, the latter leading ultimately to what has been described as atrophic cirrhosis. It is true that in postnecrotic cirrhosis, whether macroscopic or microscopic, the fibrous bands are usually coarser and thicker, but in the late stage this form may be difficult to differentiate.

My point is, and has always been, that when the shrunken, fibrotic stage occurs a vascular crisis is present, with its resultant varices and hemorrhage, as well as ascites. Much may be learned also from the site of venous obstruction, that is, whether pre- or postsinusoidal.

The lymphatic system is perhaps at fault in chylous ascites. In early nutritional cirrhosis the liver is large and transudative ascites is not present but chylous ascites occurs. The explanation is not entirely clear; 60% to 70% of ingested fat is transported by the lymphatics, and 30% to 40% by the capillaries to the portal circulation. About 5% to 6% of fat is stored in the liver, but in dietary aberrations and following noxious agents this may rise to 50% to 60%. A glance at

Rouvière's "Anatomy of the Lymphatic System" will show the enormous volume of the superficial and deep lymphatics of the liver. It is noteworthy that in both our cases the lymph nodes were greatly enlarged, and the retroperitoneal space, as well as the peritoneal cavity, contained chylous fluid. In these cases there was only about 300 to 350 cc. of this fluid, but in both the condition was misdiagnosed. The symptoms, signs, and laboratory tests of early cirrhosis were not there, but the livers were enlarged in both instances. The first patient was thought to have acute pancreatitis or perforated ulcer, and the second showed a non-visualizing gallbladder with all the symptoms of cholelithiasis, including episodic pain. The fluids were examined and found to be chyle, on the basis of the criteria Dr. McCarthy has outlined.

Dr. McCarthy and others have referred to the possibility of transient chylous ascites following a heavy fatty meal, and in the case reported here a permanent chylous ascites resulted from a segmental ectasia of the lacteals. This appears equally true in early nutritional cirrhosis, since we do not see it in advanced cases. The question arises as to whether the condition is entirely on a basis of intra- or extrahepatic obstruction to lymphatics (lymphatic hypertension) or is due to a decrease in the concentration of fat leaving the intestine or to both, as is the case with proteins in advanced cirrhosis with ascites. In the fatty stage of nutritional cirrhosis there is no portal hypertension and no transudative ascites.

Whatever the reason, nutritional, fatty, or early Laennec's cirrhosis is reversible, and in America, since the nutritional factors revolve around alcoholism, our problem is one of nutrition.

Dr. Robert Whittlesey, Cleveland: Cases of chylous ascites are recorded in the literature infrequently enough to still be interesting to the surgeon and the internist, and to the best of my knowledge this is the only film on record of a case of chylous ascites. I compliment the authors on having the forethought to take a moving picture of an unusual condition like this.

In 1954 Drs. Ingram, Riker, and I published a summary of five cases of chylous ascites occurring in children, from the Children's Memorial Hospital in Chicago. These five cases had been culled from the charts of the previous six years and therefore led us to the conclusion that perhaps the condition, at least in children, is not as uncommon as one would gather from reviewing the literature. Since that time I have seen in consultation another case, occurring in a 5-year-old white girl.

In our series the youngest case (and the youngest case on record, I believe) was a child admitted at the age of one month, with a history of swelling of the abdomen, penis, and scrotum since the first week of life. The most interesting case we came across in the charts was a 30-month-old white child who had swelling of the penis and scrotum about the time of the six-week examination. Later this child was admitted to another hospital, where the diagnosis of chylous ascites was confirmed by paracentesis. The child was put on a medical regimen, did not respond too well, went home and got off the diet, was readmitted to the hospital, and then transferred to Children's Hospital. At laparotomy, approximately 500 ml. of chyle was found. Through reinstitution of a medical regimen, with further instructions and close supervision, the child got well.

Another case was handled by Dr. Riker. Here, chylous ascites was discovered in the course of a herniorrhaphy on the right side. The herniorrhaphy was done and the child sent home, to return for repair of a left hernia six months later. At that time a saphenous-peritoneal venous shunt was accomplished, using the hernial sac to connect to the saphenous vein, which was turned back up. The child did well after that and had no recurrence of ascites.

Although the question of continued patency of this shunt has been questioned, Dr. Riker insists that it remains open.

Dr. Carl Davis Jr., Chicago: I, too, have enjoyed this presentation by Dr. McCarthy. I should like to make a few remarks regarding a case that we had approximately four years ago.

A review of the literature suggests that it is quite unusual to find free chyle in the peritoneal cavity associated with acute abdominal pathology. In most of the cases previously reported, as in our case, the presence of chyle was not suspected preoperatively. Various surgical conditions have been found at operation with free chyle in the peritoneal cavity.

It has been suggested that chyle free in the abdominal cavity acts as an irritant, as does free blood, which produces signs of acute peritonitis. In most instances it is impossible to locate the break in the lacteals, and consequently surgical treatment is directed toward the removal of the offending etiological condition.

Drainage of the peritoneal cavity is advocated in cases in which trauma has resulted in laceration of the duct of the cisterna chyli.

(Slide) The first slide depicts the condition of the abdomen in a 52-year-old patient who entered the hospital with signs and symptoms of acute small-bowel obstruction of approximately 24 to 36 hours' duration. She had had an appendectomy and a surgical exploration for small-bowel obstruction at another hospital some years before. You can see two dilated loops of small bowel, which suggest an early small-bowel obstruction.

(Slide) At operation a most interesting finding was observed. When the peritoneal cavity was

opened, a large amount of free chyle escaped over the drapes, and from 350 to 400 cc. of free chyle was aspirated. The cause of this, apparently, was a rupture of the lacteals in this area as the result of a taut, fibrous band which constricted the mesentery and this segment of the jejunum. Simply relieving this band and turning back the bowel to its normal position resulted in relief of the obstruction.

Of interest is the dissemination of chyle through the mesentery of the small bowel. There were also numerous other patches of chyle located subserosally.

This patient made an uneventful recovery. The possibility of drainage was not entertained. She left the hospital on the 11th postoperative day, free of any complications.

Dr. Harry H. McCarthy, Omaha: I would like to thank the discussants for the additional cases they have presented; I am acquainted with them.

As in the second and third cases, the cause is usually obvious. Our second and third patients had large retroperitoneal tumors, which were inoperable. These patients are still alive seven and nine months, respectively, following radiation therapy.

The first patient, who experienced the peculiar pleural effusion of unexplained origin, seven years prior to his chyloperitoneum, is living and well, three years following operation.

The fact that this man did not improve after the first laparotomy, the absence of any other explanation for the chylous ascites, the presence of the pleural effusion previously, and the presence of a diseased jejunum speak for an unusual type of chylous peritoneum. Since the patient is still well, three years after operation, there is indication that the cause of the ascites was the diseased jejunum.

Experimentally, chylothorax can easily be produced, but it is impossible to produce chyloperitoneum. We have attempted, using many different methods, to reproduce the syndrome, but we have been unable to do so.

# Early Operation for Acute Cholecystitis

C. ALLEN WALL, M.D., and ROBERT M. WEISS, M.D., St. Louis

It is well established that the ideal method of management for acute cholecystitis is removal of the diseased gallbladder. However, controversy still exists as to the best time for operation and the extent of the operative procedure during the phase of acute inflammation.

The controversy may be brought into focus by certain questions. First, is there an optimum period of time that should elapse from the onset of symptoms of acute cholecystitis to removal of the diseased gallbladder? This is to say, when during the acute phase may cholecystectomy be accomplished efficiently and expeditiously, with minimal morbidity and negligible mortality?

Second, with present advancements in surgery, is it still necessary to "stage" the operative procedures incident to removal of the inflamed gallbladder? This question brings up the relative merits of cholecystostomy and cholecystectomy, which have been thoroughly discussed in many publications.[5-10] Moreover, it includes the problem of common-duct exploration in the face of acute cholecystitis.

It is our purpose to discuss these problems from an analysis of 642 patients with acute cholecystitis.

## Case Material

For the 11-year period from 1945 through 1955, there were 642 patients admitted to the St. Louis University Hospitals with a definite clinical picture of acute cholecystitis. Operation was not performed in 174 patients. The remaining 468 patients underwent operation at varying intervals after entry.

Seventy-eight per cent of the patients were under 60 years of age, and 22% were 60 years of age or over.

In nearly two-thirds of these patients, onset of symptoms had preceded hospitalization by at least 48 hours. In 6% of the cases, symptoms existed for over 96 hours prior to entry into the hospital. In 410 patients, the usual supportive measures were employed for at least 24 hours. This number included, of course, the 174 patients who were never operated upon and 236 patients whose operation was deferred more than a day after entry. Three patients were considered moribund on entry and died during the first day despite vigorous supportive therapy.

## Results

Perforation of the gallbladder had occurred in 7% of the 468 patients who came to operation. The relation of perforation of the gallbladder to duration of the disease process is illustrated in Table 1.

Cholecystostomy was performed in 46 patients (Table 2). The remaining 422 patients underwent cholecystectomy. The common duct was explored in 168 patients. Stones were recovered from the duct in 88 patients, slightly more than half of those explored and 19% of the total number of patients managed surgically.

TABLE 1.—*Perforation in Relation to Duration of Disease*

| Onset of Symptoms to Operation, Days | Number of Patients | Perforation of Gallbladder, No. Patients |
|---|---|---|
| 0 to 2 | 32 | 0 |
| 3 to 4 | 104 | 4 |
| 5 to 7 | 96 | 14 |
| 8 to 14 | 101 | 9 |
| 14 plus | 135 | 5 |
| | 468 | 32 (7%) |

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Read at the 15th Annual Assembly of the Central Surgical Association, Columbus, Ohio, Feb. 21, 1958.

TABLE 2.—*Cholecystostomy in Relation to Duration of Disease*

| Onset of Symptoms to Operation, Days | Number of Patients | Cholecystostomy, No. Patients |
|---|---|---|
| 0 to 2 | 32 | 1 |
| 3 to 4 | 104 | 18 |
| 5 to 7 | 96 | 21 |
| 8 to 14 | 101 | 5 |
| 14 plus | 135 | 1 |
| | — | — |
| | 468 | 46 (10%) |

TABLE 3.—*Mortality in Relation to Duration of Disease*

| Onset of Symptoms to Operation, Days | Number of Patients | Deaths No. Patients |
|---|---|---|
| 0 to 2 | 32 | 0 |
| 3 to 4 | 104 | 2 |
| 5 to 7 | 96 | 6 |
| 8 to 14 | 101 | 2 |
| 14 plus | 135 | 1 |
| | — | — |
| | 468 | 11 (2.3%) |

Operative cholangiography was attempted in 59 patients; satisfactory results were obtained in 76%.

Eleven deaths occurred among the 468 patients who came to operation, for a mortality rate of 2.3% (Table 3). In addition, three patients admitted in extremis with perforation of the gallbladder died shortly after hospitalization. Of the operative deaths, which included all deaths up to six weeks after operation, there were five in patients over 70 and five in patients over 80 years of age. A single death under 70 years of age occurred in a 33-year-old man with muscular dystrophy, who died of respiratory failure soon after operation. Four deaths occurred after cholecystectomy; seven, after cholecystostomy.

## Comment

The pathogenesis of acute cholecystitis may be divided into three phases.[1,2] There is the initial obstruction of the cystic duct, followed by secretion of mucus and increased intravesical pressure, leading ultimately to the final phase of vascular obstruction and gangrene.

In this series, obstruction of the cystic duct was found at operation in 81% of patients with progressive symptoms for more than four days. This obstruction was due to multiple small stones in three-fifths of the patients and to a single calculus in two-fifths.

In the second phase, with increasing distention of the gallbladder despite appearances compatible with an infectious process, there is little bacteriologic evidence to support such an hypothesis. In 16 patients from this series operated on within the first 48 hours of the disease process, there were no positive cultures obtained of the gallbladder bile. In 43 patients in whom operation was performed between 48 to 96 hours after the onset of symptoms, there were only four positive cultures. This is in contrast to positive cultures of gallbladder bile which were obtained in 25 of 33 patients in this series in whom the interval from onset of symptoms to operation was at least six days.

Advanced changes typical of gangrene of the gallbladder were seen in 38% of the operative cases, with perforation in 7%. In 19 patients with perforation hospital management had been employed for at least 72 hours. Empyema, on the other hand, was present in only 9%.

In the nonoperative management or preoperative preparation of patients with acute cholecystitis, considerable reliance has been placed on antibiotics. Our own series shows no difference in incidence of perforation or empyema between those treated with antibiotics and those not so treated. This is not unexpected in view of the demonstration that minimal amounts of systemically administered antibiotics are found in gallbladder bile, with obstruction of the cystic duct.[3]

A properly executed medical regimen seeks to accomplish two objectives. The primary aim is to stabilize the patient's general condition from the systemic manifestations brought about by the local proc-

ess. A second objective is assistance in overcoming the inciting cause.

One may reasonably conclude that the medical regimen adopted for these patients was often ineffective in warding off perforation, with its 25% mortality. The inability to affect progression of the disease is consistent with a process that is primarily one of obstruction. Moreover, the disease is a recurrent one, since in the 468 patients operated on there were 176, or 38%, who had been hospitalized previously with a similar attack. In 18 patients, acute cholecystitis developed subsequent to cholecystostomy, performed from 4 months to 22 years before.

There is little rationale for comparison of the morbidity and mortality of cholecystostomy with those of cholecystectomy in acute cholecystitis. Cholecystostomy, generally reserved for the elderly, poor-risk patient with advanced local disease, would appear by comparison, in this series and in others, to entail greater operative risk. Of course, this is not the case.

Likewise, one expects the patient with advanced age to be an additional operative risk. Nine of the eleven postoperative deaths in this series occurred in patients over 70 years of age. Cardiovascular complications accounted for seven of these.

Although the mortality in the surgically managed patients was only 2.3%, 9 of the 11 deaths were in patients with symptoms of more than 96 hours' duration. There were no deaths in patients with onset of symptoms less than 48 hours prior to operation.

The aim in the surgical management of acute cholecystitis is the performance of an adequate operation with minimal morbidity and negligible mortality. It occurs to us that the decision for operation is perhaps best judged on the duration of disease rather than the response to a specified period of medical management. This approach is based on the recognition that prolonged obstruction will incite vascular changes, with the sequelae of gangrene. With this in mind, acute cholecystitis was evaluated with particular attention to the duration of disease from onset of symptoms to operation.

Most of the operations in this series included cholecystectomy. This would appear to be distinctly preferable to cholecystostomy if it can be done with reasonable risk. It must be remembered that the morbidity and mortality of cholecystostomy are increased by the secondary operation which may be required. Similarly, a cholecystectomy without exploration of the common duct may leave behind choledochal stones that will necessitate later exploration.

If, as we believe, acute cholecystitis is generally an incident in the course of chronic cholecystitis, there should be a comparable incidence of associated stones in the common bile duct. Acting on this premise, the common duct was explored in 36% of the 468 patients, as contrasted with an exploration rate of 43% in elective cholecystectomy during the same period. Stones were recovered from the common duct in 88 patients (19%) with acute cholecystitis, as contrasted with a recovery rate of 22% in choledochal exploration during elective cholecystectomy.

In all but one patient with choledocholithiasis, there were multiple stones in the gallbladder. No stones were recovered from the common duct in patients with acalculous cholecystitis. The one patient whose common duct contained stones in the presence of a single large gallbladder calculus had choledochal exploration because of jaundice. In the absence of jaundice, one might be fairly comfortable in omitting choledochotomy for patients with a single large stone in the gallbladder.

However, absence of jaundice in itself is not a deterrent to choledochotomy. Sixty-four of the eighty-eight patients with choledochal stones had never been jaundiced during their acute illness.

One cannot discuss choledochotomy without mentioning operative cholangiography.

This has been widely used in elective surgery of the biliary tract,[12] and we feel there is a place for it in acute cholecystitis.[13] Fifty-nine patients had the advantage of this maneuver, with satisfactory films for diagnosis in about three-fourths of the cases. Despite certain technical problems in its use during operation for acute cholecystitis, it should be kept in mind particularly as a guard against retained stones following exploration of the common duct.

From reviewing our data, it appears that these patients did well if operation was performed during the first three days after onset of symptoms. Time should be taken to correct deficits of fluid and electrolytes, but even a vigorous "medical" regimen is no insurance against perforation of the gallbladder. Although cholecystostomy may be as much as one will feel warranted in doing at operation, it appears that earlier resort to operation will diminish the incidence of perforation and permit cholecystectomy without undue elevation of the operative mortality. Similarly, with patients being brought to operation earlier and in better condition, a truly definitive operation, even including choledochotomy when indicated with cholangiography, may be permissible. This is not, of course, to advocate a foolhardy attempt at clearing the common duct of stones when the patient's condition is so critical that the immediate problem of saving life is best solved by simple cholecystectomy, or even cholecystostomy. A reoperation for retained choledochal stones is infinitely preferable to a reoperation for common-duct stricture incurred by injudicious operation under adverse conditions. There is no rule of thumb to take the place of sound surgical judgment in each individual case.

## Summary and Conclusions

Of 642 patients with acute cholecystitis, 468 (73%) were treated by operation, with a mortality of 2.3%.

Perforation of the gallbladder occurred in 32 patients, with a mortality rate of 25%. In contrast, the mortality among the remaining operative cases was 0.7%.

Early resort to operation was associated with a lower incidence of perforation and a lower mortality.

Cholecystectomy is preferable to cholecystostomy, which was necessary in 10% of the operative cases. The incidence of perforation and of cholecystostomy was highest between the fourth and the seventh day of illness.

Choledochotomy was employed in 168 of the 422 patients who had cholecystectomy. In over half of these patients (88) stones were recovered from the common duct.

Operative cholangiography served a useful function in the management of acute cholecystitis, as it does in the elective operations on the biliary tract.

The decision for prompt definitive operation is perhaps best judged on the duration of disease from onset of symptoms to hospitalization rather than the response to a specified period of medical management.

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## DISCUSSION

DR. DEWARD O. FERRIS, Rochester, Minn.: I wish to commend Dr. Wall for his excellent presentation, and to say that I agree.

In cases of acute cholecystitis, I believe that operation should be performed as soon as adequate preoperative preparation has been carried out. I am opposed to the so-called conservative or expectant treatment in this treacherous disease, which displays such great discrepancies between clinical signs and pathologic changes.

Cholecystectomy is the operation of choice in most cases, with exploration of the common duct if indicated. Occasionally the extrahepatic ducts are almost completely obscured by dense, edematous, inflammatory reaction. I have found that, despite reports to the contrary, operative cholangiography is perfectly safe in these cases. The information gained may suffice to make exploration of the common duct unnecessary, and thus a difficult and treacherous dissection may be avoided.

DR. CECIL G. MCEACHERN, Fort Wayne, Ind.: I, too, would like to congratulate Dr. Wall on his excellent presentation.

The surgical treatment of acute cholecystitis still remains a controversial subject; but, as time goes on, it is being more widely accepted as the policy of choice. The time of surgery has been widely debated. The term "early surgery" has been defined differently by different surgeons. We have defined "early surgery" as the surgery performed shortly after the diagnosis is established and the patient so prepared as to be considered in optimum condition for operation, regardless of the interval between the onset of the disease and the performance of surgery.

(Slide) This series, of 177 cases, in which "early surgery," according to our definition, was performed, demonstrates the relationship between age and mortality. In this series, 100 patients were under 50 years of age, 77 patients were 50 years of age or older. There were four deaths in the group, a mortality of 2.3%. These four deaths occurred in the age group over 50. The mortality rate in this group is approximately 5.2%, whereas the mortality in the younger group, of 77 patients, was zero.

This marked difference in the mortality rates of the two groups is significant. These figures indicate the desirability of reducing the number of operations in the older age group. These are the patients with a higher incidence of complications, leading to increased morbidity and mortality, regardless of how they are treated.

Obviously, one cannot prevent acute cholecystitis after 50, but the incidence can be materially reduced if those patients with attacks of acute cholecystitis are operated on when they first begin to experience the attacks and, second, if the patients who have cholelithiasis are treated surgically when the disease is first discovered.

We, too, have used operative cholangiography in 35 cases of acute cholecystitis and have found it to be a useful adjunct, with no demonstrable deleterious effects from its use.

In our experience, early surgery is the treatment of choice, and we believe that this may be performed at any time after the onset of the disease, after the patient has been rendered in the best possible condition for operation.

DR. ROBERT E. L. BERRY, Ann Arbor, Mich.: Dr. Wall's presentation has been excellent, and he is to be congratulated upon his results. In discussions of this type, however, it is essential that someone take the opposite point of view, not in any way to demonstrate that the essayist is wrong, but constantly to interject a word of caution about "routine" attempts to remove an acutely inflamed gallbladder. Taking out the acute gallbladder in a large University Hospital, where it is reasonable to anticipate good anesthesia, an efficient blood bank, and an extra pair of hands if needed, may indeed be a different proposition than a similar attempt in a small community hospital.

For those who have the responsibility of teaching medical students and training residents, it is important to emphasize that the operation of choice is the "safest" operation compatible with available medical facilities and the skill of the surgeon. Certainly this means that cholecystostomy often accomplishes the desired therapeutic effect without the undue, and even unnecessary, hazard to the patient that could accompany cholecystectomy.

In Michigan, for example, about 75% of all gallbladders are removed by physicians who have had no formal consolidation of their surgical training as manifested by a certificate from the American College of Surgeons or certification by the American Board of Surgery. This does not mean that the majority of gallbladders are being removed by surgeons poorly equipped for the job, but it can well mean that certain physicians will find themselves operating because there is no one else to do it. Certainly, for them cholecystostomy could well be a safer operation in many circumstances.

This excellent paper has again emphasized the practicability of cholecystectomy in acute cholecystitis. Experience, however, dictates that cholecystostomy may well be the safest, and therefore the most practical, operation for certain severely inflamed gallbladders.

DR. C. ROLLINS HANLON, St. Louis: I also would like to commend Dr. Wall for work which represents material gathered while he was a resident, and which has been collated and presented during his period with the Armed Forces, along with Dr. Weiss, who is similarly engaged in Labrador at this time.

Dr. Wall realizes, as do all of us here, that in a subject which has been discussed so frequently it is not possible to come out with any shatteringly novel view on the subject. I don't believe Dr. Wall attempted to do that.

On the other hand, I think it is worth while to emphasize, as he has done from his analysis of our material, that acute cholecystitis is an obstructive disease, and consequently the so-called "wait and see" policy is not warranted here. It is particularly worth while to emphasize that at this time, when internists and many others besides are relying on antibiotics to treat conditions that are basically not susceptible to management by antibotics.

Dr. Wall did not have time to comment on the bacteriologic studies in these cases. Such studies were carefully done in approximately 100 cases. He did not take cultures and let them stand in the operating room overnight and then report "no growth." Failure of organisms to grow indicates that this basically is not an infectious process but is an obstructive one. During the first six days from onset of symptoms, operation, the percentage of positive cultures was negligible, whereas in patients with symptoms of more than six days' duration, I believe that 25 out of 33 cultures of the bile were positive. This is correlated with the observation that if one waits until cholecystitis is a bacteriologic problem, the incidence of perforation is extremely high.

There is a great deal of reluctance to use operative cholangiography in chronic cholecystitis, and this reluctance is heightened when acute cholecystitis is present. Actually, there should be no hesitation in using operative cholangiography in any patient with chronic cholecystitis, and one will then be more likely to employ this valuable aid in selected instances of the acute disease.

DR. C. ALLEN WALL, Washington, D. C.: I would like to thank each discussant for his comments. I might add that of the 11 who died among these 468 patients managed by operation, 9 were over 70 years of age.

# Primary Sclerosing Cholangitis

*Review and Report of Six Cases*

SEYMOUR I. SCHWARTZ, M.D., and W. ANDREW DALE, M.D., Rochester, N. Y.

Primary sclerosing cholangitis is an uncommon diffuse inflammation of the extrahepatic bile duct eventuating in sufficient widespread occlusion of these ducts to cause jaundice and other manifestations of posthepatic biliary obstruction. Sclerosing cholangitis has also been referred to as "obliterative cholangitis" and "stenosing cholangitis," but, since the obliteration and stenosis of the ducts are the result of a thickened duct wall, the term "sclerosing cholangitis" more accurately connotes the disease process. A review of the literature revealed only 13 cases which were acceptable for classification as primary sclerosing cholangitis. The surgical management of six cases in Rochester, N. Y., during the past 10 years suggests that the disease is commoner than previously considered, and therefore its recognition and therapy assume greater significance. While many questions regarding the etiology, course, and final prognosis remain speculative, review of the literature coupled with a study of these recent experiences suggests certain conclusions.

## Report of Cases

CASE 1.—A 59-year-old white housewife was hospitalized July 11, 1948, with a nine-day history of increasing jaundice following an episode of right upper quadrant pain. She had experienced similar pains on seven occasions during the previous seven years but was never jaundiced. On admission her temperature was slightly elevated, and she was icteric. The liver was palpable 3 fingerbreadths below the costal margin. The stools were acholic. Laboratory findings included white blood cell count 18,000, icterus index 93, and amylase 1600 units.

Exploration was done on July 17, at which time the gallbladder, common duct, and hepatic ducts were found to be thickened. The gallbladder was small and contained no stones. The pancreas was indurated. The common duct was probed in all directions. The lumen was markedly narrowed but contained bile. A small catheter was threaded through the ampulla. The patient's jaundice subsided rapidly, and she was discharged on July 30, at which time the icterus index was 20. The catheter was removed on Sept. 2, and the patient remains asymptomatic and without jaundice.

*Comment.*—This case represents the only instance in which primary sclerosing cholangitis was associated with acute pancreatitis. Drainage of the common duct afforded prompt relief. The patient was followed for eight years, with no evidence of recurrence.

CASE 2.—A 57-year-old white man was hospitalized March 6, 1951, after three days of numbness and weakness of the right side of the body. Four weeks previously there had been a respiratory infection with nausea, and three weeks previously the urine had become dark and the stools light. He began to notice jaundice gradually increasing, followed by some itching. The past history showed typhoid illness as a child. He was known to have diabetes, of six years' duration.

He was afebrile but icteric, with a liver palpable 2 fingerbreadths below the ribs. Admission laboratory findings included white blood cell count 10,600, 4+ reaction for glycosuria, icterus index 40, alkaline phosphatase 18 Bodansky units, and 2+ stool guaiac reaction on three occasions.

The icterus index decreased to 23, and on March 21, 1951, he was operated upon. The liver was normal, and the gallbladder was thin-walled and did not contain stones. There was a chronic inflammatory reaction around the common bile duct, but the bile within was clear. When the duct was opened, its wall was seen to be markedly thickened, with an internal lumen estimated at 2 mm. A No. 6 ureteral catheter was passed through the

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sphincter of Oddi into the duodenum with considerable difficulty. After dilation a No. 12 F. T-tube was placed into the common duct for external biliary drainage. After operation he received oxytetracycline U. S. P. (Terramycin) and penicillin, magnesium sulfate, and 100 mg. of cortisone daily. The icterus index gradually decreased, and on the ninth postoperative day a cholangiogram showed a nonobstructed common duct which had a very small lumen (Fig. 1). Cholangiography was repeated on the 22d postoperative day, at which time the common duct was still quite small (Fig. 2). On the 41st postoperative day cholangiography revealed a normal duct system (Fig. 3). The T-tube was removed,

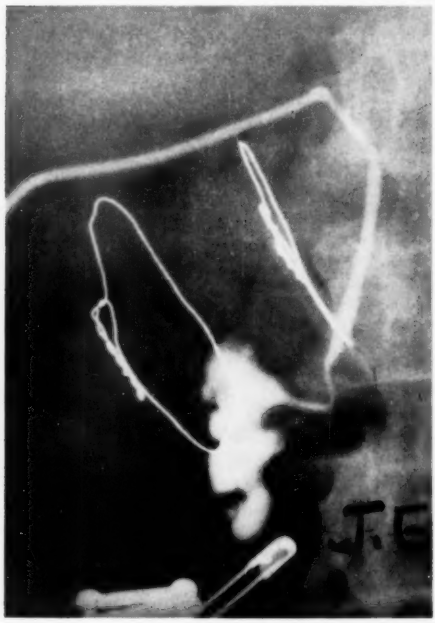


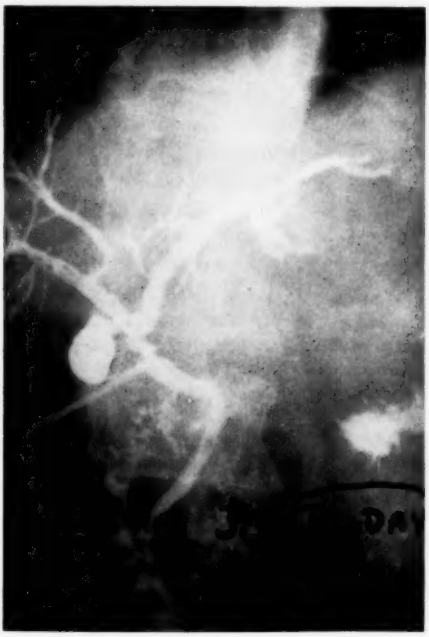
Fig. 1. (Case 2).—Cholangiogram on ninth postoperative day, showing narrowed common duct and inability to fill hepatic ducts.

and he was discharged, with a normal icterus index. He continued on 50 mg. of cortisone daily for 60 days after operation. There were two brief episodes of jaundice with symptoms of gastroenteritis during the next year, but after this no further jaundice. He died on April 7, 1955, four years after discovery of the sclerosing cholangitis, of advanced Kimmelstiel-Wilson disease with a terminal episode of pulmonary edema.

*Comment.*—Sclerosing cholangitis was unsuspected until operation, at which time external biliary drainage was carried out

Fig. 2 (Case 2).—Cholangiogram on 22d postoperative day, showing increase in lumen of distal common duct. The hepatic ducts could not be filled.

Fig. 3 (Case 2).—Cholangiogram on 41st postoperative day, showing common and hepatic ducts with some blunting of the hepatic radicles, indicating chronic obstruction.



with a T-tube. Cortisone was used for 60 days postoperatively. Despite the minor episodes of jaundice in the next year, it was thought that the sclerosing cholangitis was not associated with his eventual death, four years later.

CASE 3.—A 34-year-old white man, a physician, was hospitalized April 17, 1953, with a one-day history of nausea, epigastric discomfort, and jaundice. Questionably he had experienced two previous episodes of asymptomatic icterus at ages 15 and 20. He was afebrile but icteric. The liver was palpable 2 cm. below the costal margin on deep inspiration and was slightly tender. The gallbladder failed to visualize with oral cholecystography, and the gastrointestinal series was negative. The white blood cell count was 5400 per cubic millimeter; the urine showed a positive foam test; the stool was clay-colored and guaiac-negative; the icterus index was 48, and the alkaline phosphatase was 25.2 Bodansky units. The cephalin flocculation showed a trace, but other laboratory determinations were not remarkable.

Jaundice increased, and there was an episode of acute pain in the right upper quadrant on the third hospital day. On the fourth hospital day surgery was performed, with a preoperative diagnosis of common-duct stones. The gallbladder was enlarged, with a thickened wall, but there were no calculi in it or in the common duct. After considerable dissection a tiny common duct was located. It required dilation before the smallest available T-tube could be inserted. An operative cholangiogram showed the entire common duct to have a markedly narrowed lumen. The gallbladder was removed, and cultures of the gallbladder wall were negative. Pathologic diagnosis of acute and chronic cholecystitis and cirrhosis, on the basis of liver biopsy, was made.

There was a prolonged and initially stormy postoperative course before eventual improvement and discharge. The T-tube was left in place for two months. Postoperative treatment, besides the usual supportive measures, consisted of penicillin and streptomycin, but no cortisone was given. There was gradual improvement in liver function tests.

He moved to California and was followed at the University of California Medical Center in Los Angles. In 1956, Dr. William Longmire reexplored the patient and found marked scarring of the liver and the common bile duct, which had a narrow lumen but was uniformly patent. Throughout the latter portion of that year he remained an invalid; progressive hepatic failure finally developed, and he died Feb. 13, 1957.

*Comment.*—This case represents progression of the disease with eventual death. The initial liver biopsy showed cirrhosis without any suggestion of cholangiolitis. Microscopic sections of the liver taken at autopsy revealed typical cholangiolitis, thus substantiating the consideration that "sclerosing cholangitis" and "intrahepatic cholangiolitic hepatitis" are part of the same clinical syndrome.

CASE 4.—A 25-year-old Negro man was hospitalized March 22, 1954, with a four-week history of generalized pruritis and jaundice, associated with dark urine and light stool. The history further showed a 25 lb. weight loss in a two-month period and postprandial indigestion for several days. A year previously there had been a brief episode of painless jaundice, which subsided without treatment.

He was afebrile but icteric, with a slightly tender liver palpable 1 fingerbreadth below the right costal margin. During a month of hospitalization many laboratory tests were done. The white cell count varied between 10,000 and 15,000, and the icterus index decreased from 48 to approximately 20, where it remained. The alkaline phosphatase ranged between 12 and 17 Bodansky units. Thymol turbidity and cephalin flocculation tests were always negative. A gastrointestinal series and a cholecystogram were not remarkable, since the gallbladder filled with dye and concentrated it well.

Because of continued low-grade jaundice, laparotomy was performed on April 26, 1954. The liver was somewhat enlarged but grossly normal in appearance. There were adhesions about the ampulla of the gallbladder to the common-duct region with fibrotic tissue about the common duct. The duct itself had a 4 mm. internal diameter and was involved from the hilus of the liver to the duodenum. The gallbladder was normal and without calculus. A cholangiogram showed this generalized luminal decrease. The common bile duct was closed without drainage, and the gallbladder was left in place. A liver biopsy showed normal liver tissue. The patient was discharged on the 11th postoperative day, at which time his jaundice had disappeared and the icterus index was 7.

He did well for 13 months, when he again experienced anorexia, pruritis, and jaundice, necessitating hospitalization. The icterus index was 20 and alkaline phosphatase 9.4 Bodansky units. Intravenous cholangiography did not demonstrate the bile ducts. The patient was treated with tetracycline (Achromycin) and 20 mg. of cortisone daily, and he was discharged from the hospital two months after admission without jaundice but with an icterus index of 16 and alkaline phosphatase of 12 Bodansky units.

He was readmitted to the hospital Oct. 26, 1956, with a three-week history of pruritis and jaundice and a weight loss of 30 lb. over a six-month period. Besides supportive treatment, he received 30 mg. of prednisone (Meticorten) daily and improved steadily until discharge, seven weeks later, without icterus. He was continued on prednisone for a year and in October, 1957, had remained asymptomatic and without recurrence of icterus.

*Comment.*—This case illustrates the diagnostic difficulty prior to laparotomy. Preoperative diagnoses ranged from choledocholithiasis to duodenal ulcer with inflammatory common-duct obstruction, although no ulcer had been demonstrated by x-ray. At operation a T-tube was not placed in the common bile duct because the duct was patent and jaundice was decreasing. His further course illustrates the likelihood of recurrences and management of these with adrenal cortical hormones.

CASE 5.—A 67-year-old woman was hospitalized Nov. 5, 1954, with nausea and vomiting of 2 weeks' duration, dark urine and light stools for 10 days, and jaundice, noted the day prior to admission. On examination she was icteric, and there was mild tenderness in the right upper quadrant, but the liver was not palpable. The white blood cell count was 8000 per cubic millimeter, and the urine and stools showed color changes. The icterus index was 112 and the alkaline phosphatase 14.1 Bodansky units. The cephalin flocculation and thymol turbidity tests were not remarkable. The gastrointestinal series was normal. The oral cholecystogram did not visualize the gallbladder, and calcific densities were seen in the right upper quadrant.

On Nov. 11, laparotomy was performed. The gallbladder was thick-walled and contained multiple calculi. The extrahepatic ductal system was thick-walled, and the lumen was definitely narrowed, so that the left hepatic duct could not be cannulated at all and the right hepatic duct just admitted a small probe. Liver biopsy showed periportal fibrosis with lymphocytic invasion. A catheter was placed in the lumen of the gallbladder for external drainage, and a ureteral catheter was used to drain the common bile duct.

Besides supportive treatment, the patient received 300 mg. of cortisone daily in the postoperative period. A cholangiogram on Nov. 15, showed a narrow common bile duct, but the dye went through into the duodenum. The icterus index persisted in the range of 120, although there was some bile in the stool.

The catheters were removed just prior to discharge, on Dec. 9, 1954. Oxytetracycline was discontinued, but cortisone therapy was maintained at 75 mg. daily. The icterus index became normal by Feb. 8, 1955, and cortisone was gradually discontinued.

Within a month, however, return of anorexia and jaundice was noted. The liver and spleen became palpable. On this account, cortisone therapy was reinstituted, and over a period of three months the jaundice and symptoms gradually disappeared. When attempts were made to reduce the daily cortisone dose below 25 mg., daily evidence of rising serum bilirubin and thymol turbidity were noted on each occasion. Therapy was changed to prednisone in doses of 2.5 mg. three times daily. Jaundice and symptoms again gradually regressed. She received corticotropin gel for several months, and prednisone was discontinued on Jan. 14, 1957. She was last seen in December, 1957, at which time she was asymptomatic, and there had been no evidence of recurrence.

*Comment.*—This case demonstrates the possible chronic course that the disease may run and the use of corticoids in the treatment of the multiple recurrences of symptoms and jaundice.

CASE 6.—A 49-year-old man was hospitalized April 13, 1957. Two and one-half months before admission he noted the onset of vomiting, which he attributed to an increase in alcoholic intake. Three weeks prior to admission he had mild periumbilical pain with anorexia and vomiting and noted onset of increasing jaundice. There had been two previous hospitalizations for alcoholism but no previous history of jaundice.

He was jaundiced and the liver was palpable 4 fingerbreadths below the costal margin. The laboratory findings included white blood cell count 9500, icterus index 107, cephalin flocculation 4+, alkaline phosphatase 13 Bodansky units, and failure to visualize the gallbladder. A gastrointestinal series showed coarsening of the duodenal cap and irritability of the first portion of the duodenum.

On April 22, laparotomy revealed a normal soft, thin-walled gallbladder without stones. The lymph nodes along the common bile duct were markedly enlarged, and the common bile duct was smaller than normal, with a thick wall, and contained bile which was thick with sludge. Operative cholangiogram demonstrated the narrow lumen of the common and hepatic ducts (Fig. 4). There were no stones. Liver biopsy showed cirrhosis and bile stasis. A T-tube was left in the common bile duct. In the postoperative period, besides the usual supportive measures, he received tetracycline and 100 mg. of cortisone daily. On the 14th postoperative day the cholangiogram showed an increase in the luminal diameter of the extrahepatic biliary ductal system (Fig. 5). The T-tube was

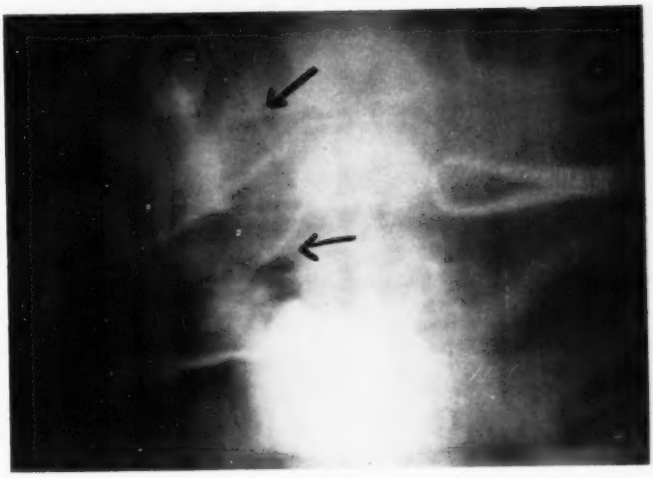
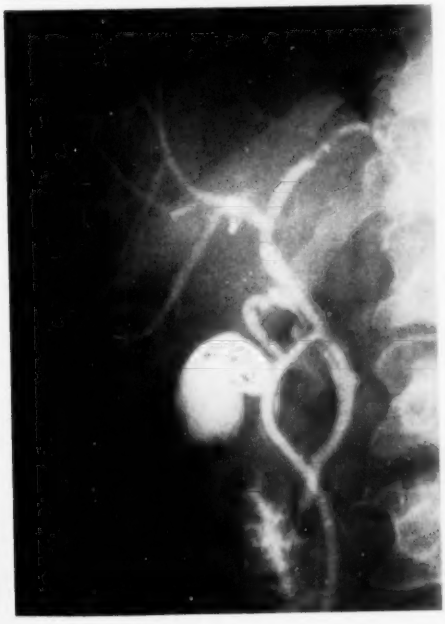


Fig. 4 (Case 6).—Operative cholangiogram, showing markedly narrowed common, cystic, and hepatic ducts.

removed the following day. His icterus gradually decreased to 14 at the time of discharge, 50 days postoperatively. Cortisone was continued for a total of 66 days and was then changed to 1 mg. of prednisone daily, which has been maintained. He was last seen in December, 1957, at which time he had remained asymptomatic.

Fig. 5 (Case 6).—Cholangiogram on 24th postoperative day, showing marked increase in diameter of lumen of common, cystic, and hepatic ducts.



*Comment.*—This case represents a rapid resolution without recurrence of manifestations of the disease. The combination of drainage, tetracycline, and cortisone resulted in marked increase in the diameter of the extrahepatic ducts two weeks subsequent to surgery, as shown by comparison of the operative and postoperative cholangiograms.

## General Considerations

*Incidence.*—In a review of the literature, difficulty arose in deciding whether certain cases previously described as instances of primary sclerosing cholangitis actually represented bile-duct inflammation due to previous surgery. Although some [1] have attached the term "obliterative cholangitis" to a significant number of cases with a similar pathologic process occurring months to years subsequent to biliary surgery, all cases with previous biliary surgery were excluded here because of the difficulty in evaluating the role of surgical trauma or infection. Inclusion of isolated segmental common-duct stricture would also have appreciably increased the incidence. Since smaller areas of stricture constitute a different problem, only instances of diffuse or generalized extrahepatic bile-duct stenosis are included. The latter group contains

TABLE 1.—*Review of Cases*

| Author | Publication Year | Age, Yr. | Sex | Clinical Findings | Operative Findings: Gallbladder | Calculi | Description | Operation | Results |
|---|---|---|---|---|---|---|---|---|---|
| Delbet[2] | 1924 | 48 | M | 2 yr. epigastric pain and vomiting; recent jaundice; stool contained some bile | Normal | 0 | Com. b. d. cord-like; bile clear | Cholecystoduodenostomy | Improved; jaundice disappeared |
| Lafourcade[3] | 1925 | 58 | M | 7 mo. jaundice; afebrile | Small; normal | 0 | Com. b. d. wall 0.5 cm. thick; many dense adhesions | Insertion of rubber tube from hepatic duct to duodenum | Died 48 hr. |
| Miller[4] | 1927 | 40 | M | 5 mo. abdominal pain; 3 wk. jaundice; stools alternated between acholic and bile-stained; slightly febrile; lab tests normal; questionable typhoid as child | Thickened wall; contained bile | 0 | Com. b. d. thickened; admitted only fine probe and contained inspissated mucus | Cholecystogastrotomy | Improved; 1 yr. mild recurrence, which subsided spontaneously |
| Whipple[5] | 1927 | 50 | F | Pernicious anemia; 1 yr. increasing jaundice; 2 mo. acholic stools | Normal, collapsed | 0 | Com. b. d. and hepatic duct all cord-like | Laparotomy | On 9th day bile was noted in stool and patient gradually improved |
| Walters[7] | 1931 | 43 | F | 2 mo. jaundice; bilirubin 15 mg. | ? | ? | Complete stricture of common and hepatic ducts | Creation of external fistula; 4 mo. later fistula implanted into duodenum | Improved; well after 3 yr. |
| Friedman[8] | 1931 | 64 | M | 4 wk. jaundice without pain | Hydrops; chronic cholecystitis | 0 | Stenosis of cystic and common bile ducts | Fistula created and 5 mo. later anastomosed to stomach | Died 1 yr. later, cause unknown |
| Ransom & Malcolm[8] | 1934 | 35 | M | 7 wk. severe right upper quadrant colic; 3 wk. jaundice; WBC 6000; bilirubin 75 mg., direct | Cholecystitis | 0 | Much inflammation around ducts; all ducts thick, narrow, containing bile | Cholecystectomy; com. b. d. brought through peritoneum | Died 4th postoperative day |
| Carter[9] | 1935 | 54 | M | Epigastric pain and 5 wk. jaundice; some bile in duodenal drainage | Distended, not inflamed | 0 | Com. b. d. thick and narrow | Cholecystogastrostomy | Died of penumonia 2 wk. postoperative |
| Vier[10] | 1951 | 38 | M | 1 mo. epigastric distress and right upper quadrant pain; no jaundice | Distended, subacutely inflamed | many | Com. b. d. thick-walled, 3 mm. lumen; bile thick and gray | 1. Cholecystectomy and insertion of T-tube into com. b. d.<br>2. 10 mo. later, Roux-Y anastomosis of jejunum to common hepatic duct | 1. Recurrence of jaundice<br>2. Asymptomatic 3 yr. |
| Werthemann[11] | 1953 | 48 | F | 3 mo. intermittent jaundice, becoming complete just prior to surgery | Inflamed | 0 | Com. b. d. thick-walled, narrow lumen; left hepatic duct stenosed | 1. Anastomosis of jejunum to hepatic duct<br>2. 5 mo. later Vitallium tube inserted into right hepatic duct, T-tube into left | Died 1 mo. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mass. Gen'l Hosp.[13] | 1954 | 21 | M | 8 mo. nausea and vomiting; intermittent jaundice | Normal | 0 | Com. b. d. enlarged, thickened, with narrow lumen; cholangiogram showed entire duct system narrow; distal common duct 1 mm. | Insertion of T-tube into com. bile duct | Died 1 day; hemorrhagic pancreatitis |
| Roberts[12] | 1955 | 59 | M | 4 mo. abdominal pain and anorexia; 3 wk. jaundice | Normal | 0 | Marked adhesions; duct cord-like; bile clear | 1. T-tube inserted into com. b. d.<br>2. 18 mo later cholecystoduodenostomy | 1. Icterus recurred<br>2. Died 18 mo.; cholangitis, cirrhosis, and pancreatitis |
| Roberts[12] | 1955 | 38 | M | 10 mo. right upper quadrant pain, nausea, vomiting, and jaundice; treated as infectious hepatitis | Normal | 0 | Duct thickened | Insertion of T-tube into com. b. d. | Improved; 1 yr. after operation, normal cholangiogram |
| New Cases | | | | | | | | | |
| 1 | | 59 | F | 7 yr. intermittent right upper quadrant pain without previous jaundice; 9 days jaundice; II * 93; amylase 1600 units; WBC 6000 | Small, thick-walled | 0 | Pancreas indurated; com. b. d. narrow, contained bile | Catheter drainage of com. b. d. | Prompt relief of jaundice; 8 yr. follow-up without recurrence |
| 2 | | 57 | M | 3 wk. jaundice; II 40; WBC 10,600 | Normal | 0 | Com. b. d. thickened with lumen estimated at 2 mm. | T-tube drainage of com. b. d. postoperative cortisone | Gradual resolution of jaundice; 2 brief episodes of jaundice during following year; died 4 yr. after operation of unrelated causes |
| 3 | | 34 | M | 1 day nausea and jaundice; II 48; WBC 5000 | Acute and chronic cholecystitis; cultures neg. | 0 | Dense adhesions; com. b. d. markedly narrowed | T-tube drainage | Jaundice gradually disappeared over 2 mo.; recurred in 3 yr.; pt. reexplored; died in hepatic failure |
| 4 | | 25 | M | 4 wk. jaundice; one previous episode of painless jaundice; II 48; WBC 10,000 | Normal | 0 | Com. b. d. with moderate adhesions; internal diameter of com. b. d. 4 mm. | Laparotomy | Improved spontaneously; 1 yr. recurrence treated with tetracycline and cortisone; 2 yr. second recurrence, treated with prednisone; continued on medication, asymptomatic 15 mo. |
| 5 | | 67 | F | 2 wk. nausea and vomiting; 1 day jaundice; II 112; WBC 8000 | Thick-walled | many small | Entire extrahepatic duct system thick-walled and narrow lumen | Catheter drainage of com. b. d. and gallbladder; postoperative cortisone | Gradual resolution of jaundice over 3 mo.; cortisone discontinued, jaundice recurred; disappeared with reinstitution of cortisone; prednisone used 2 yr., discontinued asymptomatic 1 yr. |
| 6 | | 49 | M | 2½ mo. vomiting; 3 wk. jaundice; WBC 9000; II 107 | Normal | 0 | Lumen of common and hepatic ducts narrow | T-tube; postoperative cortisone | Relief of jaundice; maintained on prednisone; asymptomatic for 9 mo. |

* II=icteric index.

TABLE 2.—*Liver Studies*

| Case No. | Blood Chemistry Findings: II * | Alk. Phosphatase, Bodansky Units | Cephalin Floc. | Prothrombin Time, % | A/G | Cholesterol Esters | Histologic Findings |
|---|---|---|---|---|---|---|---|
| 1 | 93 | 6.1 | -- | 80 | -- | -- | None |
| 2 | 40 | 18 | Neg. | 100 | 3.6/3.3 | 409/255 | None |
| 3 | 48 | 25 | Trace | 100 | 6.0/2.2 | 307/176 | Portal fibrosis; lymphocytic infiltration; bile ducts dilated, empty; diagnosis cirrhosis |
| 4 | 48 | 12 | Neg. | 90 | 3.8/3.9 | 172/112 | Normal liver biopsy |
| 5 | 112 | 14 | Neg. | 90 | 3.2/2.6 | 280/110 | Periportal fibrosis; lymphocytic infiltration; liver cells edematous with focal degeneration |
| 6 | 107 | 13 | 4+ | 90 | 4.6/3.5 | 329/35 | Fatty metamorphosis, cirrhosis, proliferation of bile ducts; deposition of inspissated bile in canaliculi |

* Icteric index.

cases in which the entire extrahepatic biliary tract is involved and also those cases in which the inflammatory process was present throughout the entire common bile duct but spared the hepatic ducts. The 13 cases which conform to these criteria of diffuse involvement are listed in Table 1. The addition of the six cases described above brings the total to 19 cases.

Most patients presented with symptoms during the fourth, fifth, and sixth decades of life. The ages ranged from 21 to 67. The ratio of male to female patients was 3:1, affording an interesting contrast to the sex ratio in acute cholecystitis, in which 80% were female.[14]

The relation of cases included in the above group of sclerosing cholangitis to others reported as cases of intrahepatic cholangiolitic hepatitis [15,16] is interesting in that the clinical syndrome is similar, but the pathologic findings in liver biopsy show a marked difference according to reported descriptions. Both sclerosing cholangitis and intrahepatic cholangiolitic hepatitis are manifest by an atypical extrahepatic jaundice. The gross findings at operation are strikingly similar, according to the descriptions which are available. Laboratory evidence of hepatic changes is summarized for the present series in Table 2. Comparison of these laboratory studies with those reported in patients with cholangiolitic hepatitis also suggests an over-all similarity. Table 2 indicates that the histologic sections of the liver in the four cases available did not show a constant pattern and in no instance could be classified as cholangiolitic hepatitis. The biopsy diagnoses varied from "normal liver" to a fairly typical portal cirrhosis (Fig. 6). This variation favors the explanation that the pathologic changes in the liver are secondary to extrahepatic biliary obstruction and cannot necessarily be used as a common denominator between cases. Over-all consideration of the factors discussed, therefore, suggests that the cases presented herein as "sclerosing cholangitis," as well as those presented elsewhere as "intrahepatic cholangiolitic hepatitis," may be representative of the same clinical syndrome. It may eventually be possible to make a further subdivision of these clinical cases which in their over-all pattern are characterized by high-grade but incomplete nontumorous and noncalculous biliary obstruction. However, for the present, cases termed intrahepatic cholangiolitic hepatitis have been omitted from the summary in Table 1.

*Etiology.*—The cause of sclerosing cholangitis is unknown. Although low-grade bacterial infection has been considered, the usual absence of systemic manifestations of infection and failure to identify an organism rule against the bacterial origin. In

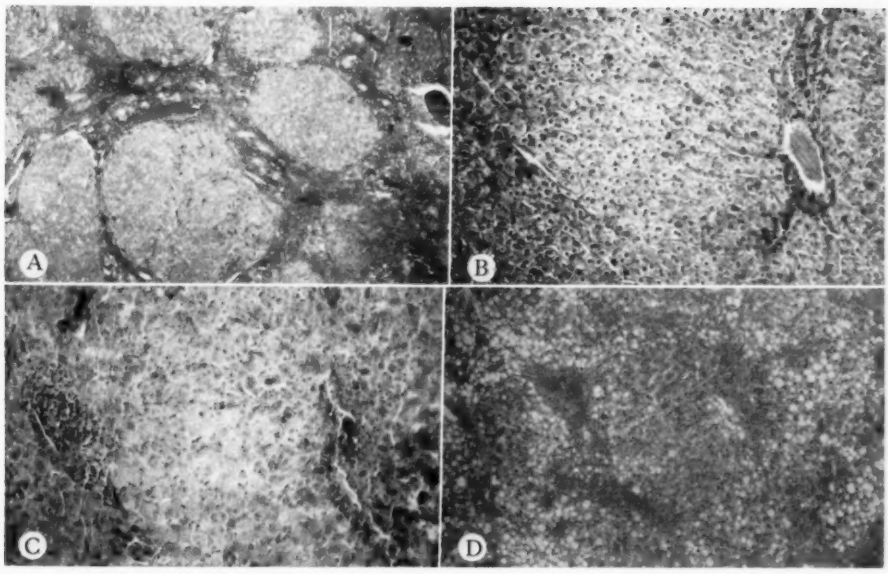



Fig. 6.—Liver biopsy tissues.

*A* (Case 3), portal fibrosis; lymphocytic infiltration; bile ducts dilated.

*B* (Case 4), normal liver.

*C* (Case 5), periportal fibrosis; lymphocytic infiltration; liver cells edematous with focal degeneration.

*D* (Case 6), fatty metamorphosis; cirrhosis.

two separate cases there was a questionable history of typhoid, but the bacilli were not recovered from the bile. Microscopic sections have shown no granulomatous lesions, and there has been no suggestion of neoplasia or metaplasia. Earlier authors [17,18] indicated the possibility that some of the cases represented the later results of congenital biliary stenosis due to ascending cholangitis during the intrauterine state. However, the appearance of manifestations of the disease in the middle and later years of life rules against this concept. None of the cases reviewed or presently reported had previous surgery, thus excluding trauma as an etiologic agent. It has also been suggested that the inflammatory process was initiated by passage of calculi through the common duct with irritation of the ductal mucosa.[19] Only in Vier's case and in one of the cases reported in this series were stones present in the gallbladder. Stones were never noted in the hepatic or common bile ducts. In many cases the gallbladder was thin-walled and showed no evidence of inflammation. Also, as will be reemphasized in the discussion of pathology, the mucosa was uninvolved.[12,13] This lack of mucosal involvement also militates against the diagnosis of an irritation due to a chemical constituent of the bile. Primary hepatic disease cannot be implicated as an etiologic factor. Biopsy shows that the liver is involved secondarily with an obstructive biliary cirrhosis. The laboratory tests of liver function have not always demonstrated hepatocellular dysfunction, and, when abnormal, they have returned to normal rapidly after the biliary obstruction was relieved.

The exclusion of all the above factors suggests the possibility that the inflammation might be the local response to a viral infection. Also suggestive are the absence of a marked temperature elevation and leukocytosis. A relative lymphocytosis with

the appearance of atypical lymphocytes has been noted.[11] Finally, microscopic sections show lymphoid hyperplasia of the regional nodes and an inflammatory response of the duct wall without marked polymorphonuclear-cell invasion.[13]

*Pathology.*—Grossly the pathologic process is a diffuse thickening of the walls of the extrahepatic biliary tract with a concomitant encroachment upon the lumen, resulting in a marked luminal narrowing. The duct system may be completely involved, or the hepatic ducts may be spared and the disease restricted to the entire length of the common duct. The gallbladder was usually not involved, and in only 2 of the accumulated 19 cases were calculi present in the gallbladder. There was no instance in which calculi were present in the common or hepatic ducts. The bile within the ducts varied from a clear yellow fluid to a thickened mucoid sludge. The lymph nodes in the region of the common duct and foramen of Winslow were usually markedly enlarged and succulent, and this entire area was encompassed in dense adhesions in several instances.

Microscopic analysis of the affected ducts showed that the walls were as much as eight times the normal thickness. The areas of inflammation and fibrosis were in the submucosal and subserosal portions, with an edematous field between them.[12] The mucosa was intact throughout and showed no change from the normal.[12,13] Biopsies of the liver revealed bile stasis and periportal fibrosis.

*Diagnosis.*—Intensive study of the cases previously reported and those presented in this paper has failed to uncover any pathognomonic sign or critical clue to preoperative diagnosis. The diagnosis is to be considered in patients, particularly those in the middle-age group, with a clinical and laboratory picture of extrahepatic jaundice. The diagnosis can be made on the basis of the findings at surgery. The first suggestion may be a dense inflammatory reaction in the region of the gallbladder and gastrohepatic ligament. This may be so intense that demonstration of the common duct is difficult, and the size of the common duct is not diagnostic because it represents the sum of a narrowed lumen and thickened wall. Palpation of the common duct, and at times the hepatic ducts, gives the sensation of a cordlike structure, which may feel like a thrombosed blood vessel. When the wall of the common duct is incised, the diagnosis should be clear. The wall is obviously thickened and cuts with difficulty, and the edges of the incision characteristically pout outward. Only a fine probe or a small Bakes dilator can be inserted into the lumen. Operative cholangiography, which vividly demonstrates the extensive narrowing of the lumen, is a useful diagnostic aid, particularly in determining the amount of hepatic-duct involvement. It also serves as a base line to follow the subsequent progression or resolution of the disease process (Figs. 2-5). It is of interest that in all cases in which operative cholangiograms were obtained the radiopaque material was seen to enter the duodenum, thus indicating that the obstruction was not anatomically complete.

*Treatment.*—The reported therapeutic approach to sclerosing cholangitis has been varied (Table 1), and treatment has consisted of procedures designed to relieve the extrahepatic block. Successful results have been achieved by means of cholecystogastrostomy, cholecystoduodenostomy, creation of an external fistula, and subsequent anastomosis of the fistula tract to the stomach or duodenum and temporary T-tube drainage of the common bile duct. Whipple's case [5] improved spontaneously after laparotomy, at which no definite procedure was carried out. Case 4 in this report improved under similar circumstances. In this instance the initial illness and two subsequent episodes were treated by means of corticoids, with complete resolution of symptoms and icterus.

A rational surgical approach is dictated by the extent of involvement of the extra-

hepatic biliary duct system. If the common duct is involved but the hepatic ducts are spared, the proximal biliary tree can be decompressed by anastomosis of the common hepatic duct or gallbladder, providing the latter contains bile, with the gastrointestinal tract. However, it seems preferable to drain the common bile duct by means of a T-tube, because it is a simpler procedure and has proved effective. If the entire duct system is involved, T-tube drainage of the common duct is also indicated. Despite the theoretic possibilities of foreign-body irritation, the insertion of a T-tube offers several distinct advantages. It affords a splint which maintains the patency of the common duct, and it offers the opportunity of following the caliber of the duct system by means of postoperative cholangiogram. If obstruction increases in the retroduodenal portion of the duct, the T-tube allows an escape vent for the bile and thus arrests the process of biliary cirrhosis. A normal gallbladder should not be removed because it may be required subsequently to shunt bile from the biliary tract to the intestine.

T-tube drainage is maintained until a satisfactory lumen is demonstrated throughout the duct system by cholangiogram, and it is apparent by clinical and laboratory examinations that bile flows readily into the duodenum. Bile salts, such as dehydrocholic acid U. S. P. (Decholin, 250 mg. three times daily), are used to increase the fluidity of the bile and therefore hydrodynamically facilitate the flow. A broad-spectrum antibiotic, such as oxytetracholine (Terramycin) or tetracycline (Achromycin), which achieves a high level in bile[19] is added to the postoperative therapy to protect against a secondary bacterial cholangitis.

The effect of corticoids on sclerosing cholangitis is of great interest. The favorable outcome in all patients who have received these drugs, and in particular the relief of symptoms and jaundice in Cases 4 and 5 during the exacerbations, prompts recommendation for its routine use. Cortisone is thought to act in two ways. First, and more important, is its anti-inflammatory effect, which by direct action on the disease process may lead to a decrease in the thickness of the walls of the bile ducts and a concomitant increase in the lumen. Second, cortisone causes a decrease in bilirubinemia. This effect has been attributed to a direct choleretic action of the drug.[20] Administration of cortisone, in doses of 100 to 300 mg. daily, is initiated immediately after surgery and continued during the period of hospitalization. Prednisone (Meticorten, 40-50 mg. daily) is preferable for long-term use, because its anti-inflammatory effect is four to five times as great as that of cortisone, with less salt-retaining potential. It should be continued for several months subsequent to the establishment of an asymptomatic patient with improved liver function tests. Recurrence of symptoms and/or icterus is indication for reinstitution of corticoid therapy.

*Prognosis.*—The outcome of sclerosing cholangitis is more favorable than has previously been considered. Although there was a mortality of 43% in the cases reviewed, it is encouraging that only one of the six cases presented in this study died, during a one- to nine-year follow-up period. The combination of surgical decompression of the biliary tract, corticoids, bile salts, and antibiotics should result in a resolution of the disease and an appreciable improvement in the over-all mortality.

## Summary

The cases of primary sclerosing cholangitis which have appeared in the literature are reviewed, and six new cases are reported.

The incidence, etiology, pathology, diagnosis, treatment, and results are discussed.

The combination of drainage of the biliary tract with postoperative use of broad-spectrum antibiotics, bile salts, and long-term maintenance on corticoid therapy is advised.

The over-all prognosis of sclerosing cholangitis is more favorable than has previously been considered.

Dr. Samuel J. Stabins, Dr. Edward W. Douglas, and Dr. Robert B. Burton permitted us to include their patients in the presentation of the case reports.

260 Crittenden Blvd. (20).

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## DISCUSSION

DR. WARREN H. COLE, Chicago: This has been an intriguing presentation. It so happens that I have seen only 1 case which falls into this category, 1 in about 125 cases of stricture, although there were 6 or 7 in which the stenosis was produced by a pancreatitis that was not related to Dr. Schwartz' report.

I think his suggestion that a virus may be the etiologic factor is a very worthy one. You will recall that he found no organisms appearing to be the causative agent. Just to make it more confusing, I want to add another etiologic factor for his consideration.

A couple of years ago Dr. Stuart Roberts, of our department, became interested in the Shwartzman reaction as it might apply to the biliary tract. As you know, the Shwartzman reaction is a sensitization reaction related to bacterial toxins. He found that now and then, at least in certain animals, one could induce the Shwartzman reaction, which would result in chronic inflammation of the common duct.

One reason why I think Dr. Roberts' results may be of importance is that Dr. Schwartz and Dr. Dale remarked that cortisone was beneficial, and one would expect cortisone to be effective in an allergic or a Shwartzman type of reaction; yet I grant that the virus possibility is a good one, also.

DR. HARRIS B. SHUMACKER JR.: I would like to congratulate Drs. Schwartz and Dale. This is such a rare condition that we certainly are badly in need of collected information about it.

I want to ask Dr. Schwartz about the duration of jaundice in his six cases. It seems to me, from the experience I had with one fatal case, that it ought to be emphasized that obstructive jaundice due to sclerosing cholangitis should be treated early. I have had no experience with the use of cortisone. If this type of management proves useful, as his experience suggests, operation should not be delayed in those cases which fail to respond to it.

I had one patient with complete jaundice of three or four months' duration in whom the common duct was obliterated. The common hepatic duct was so small that I could get only a small plastic tube into it. Cholangiograms revealed a small common hepatic and right and left main ducts with a few branches. This patient had

drainage of a negligible amount of bile during the remainder of his life. His jaundice was not improved at all, and he died of hepatorenal failure.

At autopsy, in addition to obstructive choledochitis, there was very extensive cholangiolitis, involving the smallest biliary radicles in the liver. Whether or not earlier treatment would have been effective I do not know. Since, however, the common duct was completely obliterated by the process, one might suppose that the process began here and that there might have been a stage when the intrahepatic radicles were still sufficiently patent to deliver bile to the exterior.

DR. W. ANDREW DALE, Rochester, N. Y.: Dr. Cole's suggestion is certainly intriguing and greatly appreciated.

If I may, I would like to refer Dr. Shumacker's question to Dr. Schwartz.

I arise to make one comment. Two weeks ago, in Nashville, I had the opportunity of discussing with Dr. Lynwood Herrington and Dr. William Cate a paper in which they presented similar cases before the Southern Surgical Association, and which will be published in the *Annals of Surgery*. They have called the condition in their cases "intrahepatic cholangiolitic hepatitis." From this discussion we have concluded that the clinical syndrome is quite similar. The gross pathology is very similar, but the liver biopsy findings vary in their experience, as in ours. It appears that we are discussing the same thing.

It seems to me we may be looking at a group of diseases producing a similar syndrome, in somewhat the same way that Richard Bright looked at certain kidney diseases in his day. We have hesitated for some time before presenting our experience, because we fully recognize that we know very little about this disease; but we have presented it to you in the hope that further information will now begin to accumulate.

DR. SEYMOUR I. SCHWARTZ, Rochester, N. Y.: I, too, would like to express my appreciation to Dr. Cole and Dr. Shumacker for their discussion.

In response to Dr. Shumacker's question: It was intriguing that prior to hospitalization the duration of jaundice varied from one day to six weeks. Subsequent to surgery, drainage of the common duct in most cases, and the institution of cortisone, the duration of jaundice persisted for a period varying from 14 days to 6 weeks.

I would like to add one word of caution. As we become enthusiastic in the diagnosis, we do have to become cautious. At our own institution, with our recognition of this disease, within the past two years two cases were initially signed out on our hospital records as primary sclerosing cholangitis. In these two cases autopsy was subsequently performed, and carcinoma of the common duct was found.

# Pseudomembranous Enterocolitis

*A Clinicopathologic Study of Fourteen Cases with a Common Etiologic Factor*

JOHN C. MARKLEY, M.D.; ROBERT P. CARSON, M.D., and CHARLES E. HOLZER Jr., M.D., Gallipolis, Ohio

The pathologic entity known as pseudomembranous enterocolitis has received much attention in the literature of recent years; yet a brief scanning of bibliographies on the subject will make the reader aware not only that the pathogenesis of this lesion remains an enigma but that there is a persistent trend toward identification of pseudomembranous enterocolitis with staphylococcal enteric infections secondary to antimicrobial therapy. It is evident from this study of 14 cases, first, that pseudomembranous enterocolitis is a pathologic entity not necessarily identifiable with or a sequel of staphylococcal enterocolitis, and, second, that an impairment of the blood supply of a part of the gastrointestinal tract caused by local or systemic vascular abnormalities may be a common denominator in the production of fatal pseudomembranous inflammation of the bowel.

## History

Excellent reviews have been given by Newman [1] and other authors.[2,3] Though pseudomembrane formation in the gastrointestinal tract has long been recognized as a result of the action of heavy metals and other irritants, credit is given to Finney [4] for the original description of a fatal "diphtheritic colitis" occurring in the postoperative period. In 1939 Penner and Bernheim [5] presented a study of 40 autopsies of cases of pseudomembranous enterocolitis and found that shock was a common denominator and a probable etiological factor. Dixon and Weismann,[3] in 1948, reported a series of 23 cases from the Mayo Clinic, all of which had undergone operations involving the gastrointestinal tract. An increasing incidence of the lesion was noted "in spite of the use of sulfonamides in pre-operative preparation for intestinal surgery." Kleckner, Bargen, and Baggenstoss,[6] also at the Mayo Clinic, in 1952 reported studies on 14 cases in which no surgical procedure had been performed. Observing no increase in the incidence of fatal acute pseudomembranous enterocolitis in patients treated with antibiotic or chemotherapeutic drugs, these authors did not implicate these agents in the pathogenesis of the lesion. Contrariwise, Reiner, Schlesinger, and Miller [7] in 1952 stated emphatically that chloramphenicol and chlortetracycline (Aureomycin) were the cause of the disease in seven cases observed by them.

In 1954, however, Pettet, Baggenstoss, Dearing, and Judd,[8] of the Mayo Clinic, reviewed a series of 107 cases proved by autopsy and found no statistically significant increase in the incidence of pseudomembranous enterocolitis since the advent of the antibiotic era. They emphasized the preponderance of patients who had operations for carcinoma of the colon, particularly those with obstruction, and proposed that stasis in the intestine may be an important factor in initiating or abetting the inflammatory reaction which produces pseudomembrane formation.

Concurrent with recognition of the problem of the development of resistance to antibiotic agents by certain bacteria, particularly the Staphylococcus aureus, and the hazards created by the spread of such re-

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sistant strains among hospital personnel and patients,[9-14] further attention has been focused on the S. aureus as the causative agent in pseudomembranous enterocolitis. Finland and Weinstein[9] in 1953, noted an increasing incidence of severe diarrheas in patients receiving chlortetracycline, oxytetracycline (Terramycin), and sometimes chloramphenicol. Some of these diarrheas were associated with the presence of coagulase-positive, hemolytic S. aureus in large numbers, or even in pure culture in the stools.

In 1956 Hartmann and Angevine[15] reported 17 cases of pseudomembranous enterocolitis in which the diagnosis was made at autopsy. All of the patients except one had been treated with one or more of the antimicrobial agents. Complete bacteriological studies were not carried out, but the S. aureus was found in three cases. These authors called attention to the fact that Escherichia coli is a vitamin-synthesizing organism, and S. aureus and Proteus vulgaris are vitamin-requiring organisms, E. coli being suppressed by antibiotic therapy. Thus a resulting vitamin deficiency may be responsible for pseudomembrane formation. In support of this theory, they noted that certain animals, when fed a diet deficient in pantothenic acid, developed an intestinal lesion not unlike that of pseudomembranous enterocolitis.

Weismann and Twitchell,[16] in 1956, presented 16 cases of patients who had severe diarrheas with abdominal distention, pain, and sometimes shock occurring in the postoperative period. Eight patients died, and of the six who came to autopsy a diagnosis of pseudomembranous enterocolitis was made. In the case of one of the patients who lived, shreds of pseudomembranous substance were found in the stools. The authors believed that because the milder cases resembled clinically the more severe, fatal cases, a diagnosis of pseudomembranous enterocolitis was justified. Of nine patients having antemortem stool cultures, five showed as the predominant organism the hemolytic S. aureus. They stressed the role of antimicrobial therapy and superinfection with S. aureus in the production of the disease but suggested that circulatory disturbances, release of adrenocortical hormones during surgical stress, and intestinal statis due to obstruction may increase the susceptibility of the bowel to severe infection.

Lepley and Smith,[17] reporting in 1957 a collection of 16 bacteriologically proved cases of severe staphylococcal enterocolitis, 12 of which received one or more of the broad-spectrum antibiotic agents, commented that "the relationship of this disease to the pseudomembranous enterocolitis which occurred prior to the antibiotic era has not been definitely established." They concluded, however, that most cases of enterocolitis are due to an antibiotic-resistant, virulent, hemolytic S. aureus. Judd, in his comments on their paper, noted that at the Mayo Clinic in the presence of pseudomembranous enteric disease, no specific organism could be demonstrated consistently by the most diligent bacteriological studies. He also emphasized the fatal nature of the lesion regardless of the therapy employed. In a similar vein, it was concluded in a recent editorial review[2] that pseudomembranous enterocolitis and acute staphylococcal enteritis are distinct and separate entities and, while the role of the broad-spectrum antibiotics in the production of staphylococcal enteritis is reasonably clear, it has by no means been proved that such agents either condition the occurrence or aggravate the symptoms of pseudomembranous enterocolitis.

## Material

Fourteen patients, all of those in whom the diagnosis of pseudomembranous enterocolitis was made by postmortem examination since 1952, constitute the material of this study. There were 8 men and 6 women, ranging in age from 45 to 86 years, with an average age of 69.

Seven of the patients had abdominal operations, in six of whom the gastroin-

*Age, Sex, Primary Diagnosis, Operation Performed and Circulatory Abnormality in Fourteen Patients Having Pseudomembranous Enterocolitis*

| No. | Age | Sex | Primary Diagnosis | Operation | Vascular Abnormalities |
|---|---|---|---|---|---|
| 1 | 78 | M | Volvulus—small intestine | Reduction volvulus | Partial strangulation small intestine due to volvulus |
| 2 | 45 | F | Volvulus—sigmoid colon | Resection sigmoid colon | Strangulation of sigmoid due to volvulus |
| 3 | 59 | F | Embolus—sup. mesen. artery | Resection small intestine | Embolus of superior mesenteric artery |
| 4 | 52 | M | Thrombosis sup. mesen. artery | None | Thrombosis of superior mesenteric artery |
| 5 | 82 | M | Perforation of ileum by toothpick | Closure perforation; appendectomy | Segmental stenosis of superior mesenteric artery |
| 6 | 62 | F | Biliary dyskinesia | Excision cystic duct; choledochostomy | Segmental stenosis superior mesenteric artery and celiac artery |
| 7 | 82 | F | Small-bowel obstruction | None | Arteriosclerosis, partial occlusion superior mesenteric artery; torsion with strangulation |
| 8 | 79 | M | Chronic duodenal ulcer | Gastrectomy; vagotomy | Severe arteriosclerosis mesenteric arteries, partial occlusion |
| 9 | 70 | M | Arteriosclerotic heart disease, severe | None | Partial thrombotic occlusion abdominal aorta; stenosis superior mesenteric artery |
| 10 | 78 | M | Influenza; acute arthritis | None | Partial strangulation small intestine due to inguinal hernia |
| 11 | 86 | F | Richter's hernia | None | Partial strangulation small intestine due to femoral hernia |
| 12 | 70 | M | Pulmonary emphysema; cor pulmonale | None | Cor pulmonale with anoxemia |
| 13 | 74 | M | Acute gastroenteritis; arteriosclerotic heart disease, severe | None | No abnormality |
| 14 | 49 | F | Chronic ulcerative colitis | Total colectomy | No abnormality |

testinal tract was involved, the seventh consisting of removal of a cystic duct remnant and choledochostomy (Table). The other 50% had no surgical procedure.

With one exception, at the time of their admission to the hospital all of the patients were in poor general condition because of advanced age, debilitating disease, cardiovascular disorders, acute catastrophic illness, or a combination thereof.

The manifestations of severe enteric disease in these patients were those described by previous authors, namely, abdominal cramps, distention, choleriform diarrhea with watery, green stools, which in some instances became bloody, severe dehydration with disturbance of electrolyte balance and, finally, shock. In only three cases was peripheral vascular collapse noted prior to the onset of clear-cut symptoms of severe gastroenteric disease; therefore in this series of cases no etiological significance can be ascribed to shock per se.

Significant bacteriological studies are not available in this material, since cultures were obtained from only two patients. In one case a culture of the stool at the onset of the disease showed S. aureus and coliform organisms; in the other only coliform organisms were noted. It is noteworthy, however, that staphylococci were not readily demonstrable in the stained sections, bacilli forming the predominant flora. In known cases of staphylococcal enterocolitis typical colonies of staphylococci have been noted in abundance in the histological sections.

Of the 14 cases presented, all but 1 received some form of antimicrobial therapy: 10 received penicillin, 7 streptomycin, 4 oxytetracycline, 2 chloramphenicol, 1 erythromycin, and 1 sulfisoxazole (Gantrisin). However, a study of the time relationships involved reveals that among the 13 patients receiving these agents there were only 6 in whom the antimicrobial drugs might have had an effect in producing pseudomembranous enterocolitis; the others received these drugs only after the onset of their severe intestinal symptoms or lived less than 24 hours after the institution of therapy, obviously too short a time for the production of a significant effect on the intestinal flora. Of the six cases in which antimicrobial therapy might have had an etiological relationship, one patient received only sulfisoxazole, a sulfonamide, for urinary antisepsis. One

patient who had a mesenteric thrombosis was given chloramphenicol at the onset of his symptoms, S. aureus being present in the stool culture at the time of admission to the hospital. One patient received penicillin for 3 days at home for "flu" with diarrhea and penicillin and streptomycin for 10 hours preceding his death in the hospital. Another patient was operated on for partial intestinal obstruction due to volvulus of the small bowel caused by postoperative adhesions. He received penicillin and streptomycin for four days before operation and penicillin and oxytetracycline for nine days after operation, until death. The fifth patient was given oxytetracycline and penicillin for 12 days before gastrectomy and penicillin and streptomycin after operation until death, 5 days later, symptoms of enterocolitis appearing on the 3d postoperative day. In the sixth case the patient received erythromycin for four days prior to the onset of severe diarrhea and died on the fifth day. In summary, of the 14 cases there were only 6 in which there could be any possible correlation between the use of antimicrobial agents and the development of pseudomembranous enterocolitis, and in the first three of the six cases incrimination of the drugs used is not well grounded.

Complete necropsy was carried out in each case. Often there was a small amount of bloody fluid within the peritoneal cavity, and flecks of fibrin were noted on the involved segments of intestine. The stomach, small intestine, and colon were usually dilated and filled with fluid and gas. In the more advanced cases the intestine was dark reddish-blue with mottled patches of reddish-black discoloration.

The mucosal lesions varied in size and extent from 3-mm. flecks of exudate to longitudinal, narrow, serpiginous lesions or to long, circumferential segmental areas of disease. There were surface exudates having a "membranous" or "pseudomembranous" appearance. These were elevated and shaggy and appeared necrotic or fibrinous. The color ranged from grayish-white to yellow-tan or dark red, depending upon the intestinal content. Sometimes the exudate had sloughed, leaving a shallow, denuded area, which was hyperemic, bleeding, and granular. Generally there were severe edema and hyperemia of the intestinal wall.

In five cases the small intestine was the site of extensive and diffuse involvement. In three patients the colon was primarily involved, and there were only patchy foci of inflammation in the small intestine. Two patients had diffuse, almost generalized involvement of the stomach, intestine, and colon. Usually, however, there were only scattered, superficial, hemorrhagic erosions in the stomach.

Histologically the pseudomembranes consisted of necrotic debris, fibrin, neutrophils, and mucus. The mucosa was the site of varying degrees of erosion. Sometimes only the tips of the villi were involved, but in other instances the ulcers extended into the submucosa. There were always heavy infiltrations of polymorphonuclear leukocytes in these zones. In the severer cases this inflammatory reaction amounted to frank cellulitis, with areas of suppuration or phlegmonous inflammation involving all layers of the small intestine or colon. Wherever colonies of bacteria were observed there was a mixture of bacilli and cocci, but staphylococci were never in predominance.

The striking feature presented by the findings at autopsy in these 14 patients was the predominant evidence of an impaired blood supply of a part of the gastrointestinal tract, due to a local or systemic abnormality. In two instances (Cases 1 and 2, Table) a volvulus was found involving in one case the small bowel and in the other the sigmoid colon. In the first patient operative reduction was accomplished, and in the second the sigmoid colon was resected. Pseudomembranous inflammation was found within and adjacent to the portion of bowel involved in the process of torsion. This relationship of the inflammatory lesion to ischemic bowel seems more than coinci-

dental. A third patient (Case 3) had an embolus of the superior mesenteric artery and underwent an immediate resection of almost the entire small intestine. The resected specimen showed patchy areas of gangrene and, in addition, extensive pseudomembranous enteritis. At autopsy, four days later, the same process was demonstrated in the remainder of the small intestine and in the colon. Another patient (Case 4) showed an old, recanalized thrombus with occlusion by fresh clot in a major branch of the superior mesenteric artery, producing infarction of the middle one-third of the small bowel. The area of gangrene showed typical pseudomembranous inflammation in addition to ischemic necrosis, suggesting that infarction became complete only after the onset of the inflammatory process. In addition, there were areas of pseudomembrane formation in the cecum. In two cases (5 and 6) segmental stenotic areas were noted near the origin of the superior mesenteric artery. In one of these the diameter of the vessel was reduced to 2 mm. by an atheromatous plaque; in the second a firm, white organized thrombus reduced the lumen to a diameter of 1 mm. over a distance of 5 mm. Three patients (Cases 7, 8, and 9) had severe generalized arteriosclerosis with old myocardial infarcts. The mesenteric arteries were rigid, tortuous, and generally narrowed. The degree of stenosis was deemed to be more than sufficient to embarrass seriously the blood supply to the abdominal viscera. In addition, one of these patients (Case 7) was found to have a partial obstruction of the small intestine, caused by old postoperative adhesions. Two sharply circumscribed segments of the small bowel showed pseudomembranous disease. Incarcerated herniae were found in two cases (Cases 10 and 11). In the first patient, who had an inguinal hernia, the disease involved the incarcerated segment of small bowel and the entire colon, but the free portion of small intestine showed no abnormality. In the second a loop of ileum was partially strangulated in a femoral hernia, forming a Richter's hernia. On either side of the strangulated loop the intestine showed typical pseudomembranous inflammation. Three patients (Cases 12, 13, and 14) showed no local vascular impairment. One of these (Case 12), a 70-year-old man, had a large villous adenoma of the rectum, immediately proximal to which the sigmoid colon showed extensive pseudomembranous colitis. In addition, this man had severe pulmonary emphysema with cor pulmonale producing generalized anoxia, which was regarded as a possible contributing factor in the pathogenesis of the inflammatory lesion of the colon. Patient 13, a 74-year-old man, had extensive pseudomembranous disease of the small intestine and the entire colon. Severe atherosclerosis of the abdominal aorta and mesenteric arteries was found, but there was no marked narrowing of the vessels. Patient 14 showed no evidence of vascular impairment. This was a middle-aged woman who had advanced chronic ulcerative colitis, an ileostomy, and severe malnutrition. She died 24 hours after total colectomy, and autopsy showed severe pseudomembranous enteritis of the small intestine, the process being distinct from the ulcerative lesion of the colon. Shock associated with abdominal cramps appeared four hours after the operation, probably heralding the onset of enteritis rather than constituting a contributory factor.

## Comment

A number of authors have incriminated antimicrobial therapy, with resultant superinfection with antibiotic-resistant strains of hemolytic S. aureus as the sole or principal cause of the reported cases of pseudomembranous enterocolitis. Speare[18] in 1954, presented eight cases, in five of which hemolytic S. aureus was isolated from the stool culture. He, like Hartmann and Angevine,[15] considered the disease a complication of antibiotic therapy. Newman,[1] however, as a result of an extensive review, noted: "That antibiotics are the sole cause of this

condition can easily be eliminated by a study of the literature." The experience of the Mayo Clinic is important in this regard. Pettet, Baggenstoss, Dearing, and Judd [8] found no statistically significant increase in the incidence of pseudomembranous enterocolitis concurrent with the advent of the era of antimicrobial therapy. At the Mayo Clinic, between 1925 and 1938 there were 45 cases, and from 1939 to 1952 there were 49 cases.

It has been concluded in regard to the 14 cases presented in the current analysis that antibiotics could have played no etiological role in eight cases and probably had no effect in three of the remaining six. It cannot be stated positively that the hemolytic S. aureus can be relegated to a minor role, since no adequate bacteriological examinations are available; however, staphylococci were not readily demonstrable in stained sections in these cases, and they have usually been found in profusion in cases of staphylococcal enterocolitis at necropsy. Likewise, Judd, cited earlier, noted the failure at the Mayo Clinic, in spite of the most diligent bacteriological studies, of demonstration of any specific organism in the presence of pseudomembranous enteric disease.

Attention has been called to possible etiological factors noted by other authors. Penner and Bernheim [5] found shock to be a common denominator in 40 cases and were able to reproduce pseudomembranous lesions in animals subjected to shock. In the present series of cases, shock was usually present only after the onset of severe enteric symptoms and probably played no major etiological role.

Dixon and Weismann [3] emphasized the importance of intestinal operations as a possible etiological factor. Only one-half of the patients in this study had any surgical procedure.

Pattet, Baggenstoss, Dearing, and Judd [8] called attention to the rather large number of patients in their series (26 of 94 patients) who had a severe degree of intestinal obstruction. They suggested that stasis in the bowel and impaired circulation due to distention of the wall of the intestine might predispose to pseudomembranous inflammation.

The cases reviewed in this study demonstrated in varying frequency all of the possible etiological factors suggested by previous authors, namely, previous antibiotic therapy, staphylococcal infection, intestinal obstruction, shock, and predisposing surgical procedures. None of these, however, occurred with sufficient preponderance to suggest a constant etiological relationship. There is, however, what appears to be a common denominator, namely, an impairment of the blood supply of the intestine. One patient, in addition to severe arteriosclerosis with partial occlusion of the superior mesenteric artery, had evidence of torsion of the mesentery with venous obstruction. Six patients had significant impairment of the arterial blood supply of the small bowel as a result of thrombosis or embolism of the superior mesenteric artery, segmental stenosis of the artery, or severe arteriosclerosis with general narrowing of the vessels. Four patients showed obstruction of the blood supply of the bowel by extrinsic factors (volvulus in two and strangulated hernia in two). One patient had a large villous adenoma of the rectum with partial obstruction and severe pulmonary emphysema, with cor pulmonale producing cyanosis and systemic arterial oxygen unsaturation. Significance is attached to the fact that in those cases in which the impairment of blood supply was localized, as in those with strangulated herniae and volvulus, the severest involvement with pseudomembranous disease was found in or adjacent to the ischemic segment of bowel, even though in some cases other portions of the bowel were affected.

In only 2 of the 14 cases were obvious circulatory abnormalities not demonstrated. The one was a middle-aged woman who underwent a total colectomy for ulcerative colitis after revision of her ileostomy for

dysfunction. Her general nutritional status was very poor, and prior to colectomy she had recurring signs and symptoms of obstruction of the small bowel, though no evidence of obstruction was found at operation or autopsy. The other patient was a 74-year-old man who developed severe diarrhea at the same time as his wife. He died 18 hours after admission to the hospital. No localized vascular abnormality was found, though he had extensive generalized atherosclerosis and an old myocardial infarct. It is postulated that an enteric infection which was quite mild in his wife was sufficient to set off a pathological process in nutritionally deficient tissue, producing pseudomembranous enterocolitis, fatal in its outcome.

Thus the most constant, and, in fact, a quite striking, feature of the cases reported here is evidence of impairment of the blood supply of the small intestine or colon. While it is obvious that a variety of precipitating factors must play a role, ischemia or anoxia of the intestinal wall seems to be an important or essential condition in determining that the intestinal mucosa will react to inflammation in a certain specific way, namely, the production of a pseudomembrane. An analogy may be drawn between this reaction of the intestine to infection and the production of gangrene of the skin and soft tissues by infection in a limb involved with occlusive vascular disease. The blood supply is minimal but adequate until the tissue is insulted by bacterial invasion, whereupon not only cellulitis but necrosis results from factors which would ordinarily produce only an inflammatory response in properly nourished tissues.

## Summary and Conclusions

A study of 14 cases of pseudomembranous enterocolitis proved by autopsy has revealed a common denominator which appears to be of considerable significance in the pathogenesis of the disease. Twelve of the fourteen cases showed local or systemic circulatory abnormalities capable of producing anoxia or ischemia of the intestine. The close association between the pseudomembranous process and anatomic evidence of vascular insufficiency in localized segments of bowel in many of the cases indicates that the reaction of the intestine to injury was conditioned by the impaired nutritional state of its tissue. Shock, predisposing surgical procedures, intestinal obstruction, previous antimicrobial therapy, and infection by the S. aureus, all considered by previous authors as possible etiological factors, were encountered in varying frequency, but not often enough to be considered of fundamental importance in explaining the pathogenesis of pseudomembranous inflammation of the intestine.

It is suggested, therefore, that in the light of present knowledge there is no justification for a conception of pseudomembranous enterocolitis as a specific disease entity subject to clinical diagnosis based on the appearance of a typical syndrome or on the detection of a specific etiological agent. The evidence at hand indicates that pseudomembranous enterocolitis is a pathologic entity resulting from the action of a variety of noxious factors in the presence of an underlying disorder characterized by a deficiency in the volume of blood or in the nutrient quality of the blood reaching intestinal tissue.

The Holzer Hospital, First and Cedar Sts.

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## DISCUSSION

DR. EDWARD S. JUDD, Rochester, Minn.: I believe one of the reasons Dr. Holzer invited me to discuss this very nice paper was that it has now been about four years since my colleagues and I suggested in an article in *Surgery, Gynecology and Obstetrics* that the incidence of pseudomembranous disease at the Mayo Clinic was not changing much as the years went by. That stimulated quite a reaction. Various physicians said: "That is not true. We are seeing tremendous increases in our incidence of this disease."

A rather sharp distinction can be made between the modern enteritis due to Staphylococcus aureus and the old, well-known pseudomembranous disease which the elder Finney described so beautifully before the turn of the century. It is interesting to see that Dr. Holzer and others are finding significant facts in their area, although, of course, no one individual sees many proved cases in any one surgical career.

The shock factor had been discussed thoroughly in earlier years. That, as Dr. Holzer has pointed out, is probably not the entire answer. At our University, Dr. Richard Lillehei has been doing interesting work with shock on dogs. He has been bleeding these dogs massively at intervals. Some of the dogs have had striking changes which look like the disease which Dr. Holzer has described again today.

My colleagues and I had been struck in earlier work in our own cases with the possibility that obstruction of the intestine might be a major factor in producing the disease, and in some of our cases antecedent obstruction seems likely. However, that is not the only factor, because many patients have had no such obstruction.

We, as well as everyone else, I believe, have now reduced drastically the incidence of the staphylococcal variety of this terrible complication on our various services, and we hope everyone is so alert to the possibilities that when this dread complication appears the most junior of the interns will recognize the possibility immediately, take proper steps, and discontinue the use of the offending antibiotic immediately and then start use of a proper remedial agent.

However, this is not the disease known throughout the years as pseudomembranous enterocolitis. The two clinical pictures may be identical, and also the pathologic changes may be identical, but there seems to be a sharp distinction.

It appears that the statement, made about four years ago, is substantially correct—that the incidence of pseudomembranous enterocolitis at the Mayo Clinic runs about the same from year to year. This seems to be in spite of steroid therapy, either preoperative or postoperative. We do not change the fatal issue in many instances.

The modern-day bacteriologist has striven desperately to develop media for culturing the stools, hoping to strain out those organisms which might be masking the invasion of micrococci, and he has come up with some interesting media which have been most helpful. However, in true pseudo-

membranous enterocolitis no specific agent has been proved present, to my knowledge.

DR. BEN EISEMAN, Denver: During the past year we have had rather startling success in a novel method of treating four cases of staphylococcal enteritis, such as has been described by Dr. Judd. In each case (three postsurgical and one nonoperative) the use of oral wide-spectrum antibiotics was followed by severe, life-threatening, bloody staphylococcal diarrhea, which was resistant to all methods of therapy. Reasoning that staphylococci had grown unchecked when other organisms had been removed, we reestablished a more or less normal colonic flora and fauna by simply reintroducing feces from a normal person into the patient via a saline enema. We had a little difficulty in convincing the nursing service to carry out these orders. We administered such enemas every four to six hours, and in each of the four cases the diarrhea stopped and staphylococci disappeared from the stool as E. coli and other organisms returned.

This small series is obviously too limited for us to draw any conclusions, but the therapeutic results were so striking that I mention it in the hope that others in the Association will give this simple procedure a trial, so that a more adequate evaluation of its efficiency can be made.

DR. JOHN A. GIUS, Iowa City: I should like first to congratulate Dr. Holzer and his associates on this very nice presentation. I must confess that Dr. Eiseman stole my thunder a bit.

I had the privilege recently of hearing a report by Dr. Herbert H. Kersten, of Fort Dodge, Iowa (J. Iowa M. Soc. 48:240 [May] 1958), who has given me permission to relate it to you. Dr. Kersten discussed the importance of certain biological relationships in the production of the syndrome which we currently call pseudomembranous enterocolitis. He drew an analogy between this condition and the changes which have been observed in the grasses of the Kalsow prairie in northwestern Iowa.

This area has never been under cultivation, and the grasses which grow there have been the same for centuries. There have been no sprays or fertilizers to change their growth pattern or biologic balance, whereas in adjoining regions, where cultivation has been carried out for a long time, weeds of all types grow and man fights a constant battle against them.

Now, in the intestinal canal (and perhaps in all other areas as well) when the normal biologic relationships are upset by antibiotics or other influences, a veritable vacuum is created. Here resident or transient bacteria, or perhaps submicroscopic organisms, which in the normal state are inhibited and cause no difficulty, find a favorable environment for growth and invasion. This seems to me to be a very apt analogy.

Dr. Kersten's patient was a short, obese woman with a partially obstructing carcinoma of the sigmoid, who, after preparation with neomycin, had an anterior resection. On the sixth day she developed violent dysentery and all the typical findings of this syndrome. This led to severe shock, and she soon appeared moribund. The liquid stools continued in spite of all measures until the 11th day, when she was given an enema derived from another hospital patient. Within six hours the stools became more normal in character, her condition improved rapidly, and ultimately she made a satisfactory recovery.

This, of course, proves nothing, but suggests that the upsetting of normal biologic relationships which exist between bacteria and the host may be of great importance in the production of this syndrome. Further studies in this area are needed.

DR. KENNETH E. LEMMER, Madison, Wis.: Apropos of what Dr. Eiseman has said, at the University of Wisconsin we are very close to the agricultural department. When cattle develop a condition of this type, namely, an enteritis, on antibiotic therapy, the department does do the same sort of thing except that they put the feces in capsules and feed it from the top.

I have been trying for some time to get our bacteriologists to mix up capsules of cultures of normal intestinal flora for me, and we have grown these organisms. We are now waiting for a patient on whom to try it. We have not taken the raw material and put it in the capsules and given it to patients, but we have considered doing it. Probably the method suggested by Dr. Eiseman is better.

DR. JOHN C. MARKLEY, Gallipolis, Ohio: I am glad to see that we have stirred up a bit of a hornet's nest about this problem. I would like to thank each of the discussers for their comments and would say a loud "Amen!" to what Dr. Judd has said about the whole problem.

As was pointed out by Dr. Holzer in this paper, we do not believe that the antibiotics used or a particular organism represents the crux of the problem. There is evidence that the incidence of the disease is not increasing. On the other hand, I would wager that the use of broad-spectrum antibiotics is increasing. These items suggest that there is no firm connection between the use of broad-spectrum antimicrobial agents and the occurrence of pseudomembranous enterocolitis.

Dr. Eiseman, Dr. Gius, and Dr. Lemmer have certainly presented a novel way of treating this disease. I can well imagine Dr. Eiseman's difficulty in convincing the nursing staff that they should give the end-results of one patient to another patient on the same ward.

I would like to emphasize one point. We believe that the differentiation of staphylococcal enterocolitis and pseudomembranous enterocolitis is well nigh impossible. In the literature there are a number of reports in which investigators have analyzed the records of patients surviving this disease. The diagnosis is based upon the presence of fever, abdominal pain, shock, and the growing of a pure culture of Staphylococcus from the stools. This has been called pseudomembranous enterocolitis. There is actually little difference between the manifestations of pseudomembranous disease and staphylococcal enterocolitis. Finding staphylococci in the stools establishes only that the infection is staphylococcal but does not necessarily mean that pseudomembranous disease exists. The latter seems to be a pathologic diagnosis. We feel, therefore, that reports of so-called survivors of pseudomembranous disease must be regarded with skepticism, since these survivors probably include a number of persons with staphylococcal enteritis.

In connection with the problem of staphylococci, we have pointed out that we have been unable to find this organism in our stained tissues, at least not in any preponderance. We feel, therefore, that almost any pathogenic organism under the proper circumstances is capable of causing this condition. We wish to reemphasize the main point of our paper, namely, the importance of defects of intestinal vascular supply or venous drainage, regardless of its cause.

We certainly shall keep in mind this novel method of treating the disease with enemas. I wonder if buttermilk by gastric drip might not accomplish the same sort of thing.

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# Acute Nonclostridial Crepitant Cellulitis

W. R. CULBERTSON, M.D., Cincinnati

The discovery of gas in infected tissues is usually very alarming, since gas gangrene is immediately suspected. However, on further clinical and laboratory investigation, it may be found that infection by virulent clostridial organisms has not occurred and that acute nonclostridial crepitant cellulitis is the real cause.

Associated with cellulitis, subcutaneous emphysema may be caused by the following factors:

I. Extrinsic factors
  A. Physical introduction of air by
    1. Severe trauma (with partial avulsion)
    2. Improper irrigation of wounds
    3. Injuries involving the organs of respiration
  B. Chemical generation of gas
II. Intrinsic factors
  A. Infection by aerogenic bacteria
    1. Clostridial bacteria
    2. Other bacteria

The infected wound may possess gas introduced extrinsically by physical means, such as severe trauma, improper irrigation of wound, injuries involving respiratory organs, or chemical generation of gas by such agents as hydrogen peroxide. Examples of this type of infection have been reported by Rubenstein, Tabershaw, and Daniels[7] and Schreus.[8]

Gas may be produced within the tissues by various aerogenic bacteria, the most frequent of which are the clostridia. Clostridial crepitant cellulitis characteristically occurs in the subcutaneous or retroperitoneal tissues and is also known as anaerobic cellulitis. Aerogenic bacteria other than the clostridia may also produce gas in subcutaneous tissues. These include three main groups: the coliform bacteria, particularly Escherichia coli and Aerobacter aerogenes, the anaerobic streptococci, and various Gram-negative bacilli of the Bacteroides group.

Acute nonclostridial crepitant cellulitis is included among infections due to "other aerogenic bacteria." It is a clinical entity and is characterized by a rapidly spreading emphysematous infection involving the skin and subcutaneous tissues and accompanied by severe toxemia. The description was first cited by Marwedel and Wehrsig in 1915, when they noted two instances of infection with subcutaneous gas caused by the anaerobic Streptococcus. Later, in 1936, Howe reported a case of emphysematous infection of the subcutaneous tissues occurring after appendectomy and spreading rapidly to involve structures as distant as the neck and thigh. Repeated cultures failed to show the presence of clostridia. In the same year Meleney reported a fourth example with a bacterial flora which included aerobic hemolytic Streptococcus, E. coli, and nonhemolytic anaerobic streptococci. Another case, in 1940, was reported by Farrell, which originated from a perirectal abscess with crepitant cellulitis involving the lower abdomen, inguinal areas, and thigh.

## Material

In a previous report,[2] data concerning a series of 12 proved cases of acute nonclostridial crepitant cellulitis were presented. Since then 12 additional cases have been observed at the Cincinnati General Hospital and the University of Cincinnati. The areas most frequently affected by widespread in-

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From the Department of Surgery, Cincinnati General Hospital and the University of Cincinnati College of Medicine.

TABLE 1.—*Site of Origin*

| | |
|---|---|
| Perineum and anus | 3 |
| Abdominal wall | 8 |
| External genitalia | 2 |
| Lower extremity | 9 |
| Chest wall | 1 |
| Oropharynx | 1 |

fection were the lower extremity and the abdominal wall (Table 1). In all but four instances the disease was preceded by either an operative wound or a relatively minor infected area which was traumatized. In only the exceptional cases was the site of origin distant from those areas likely to be contaminated by fecal or urinary-tract discharges. The youngest patient was 22 and the oldest was 89, the average age being 49 years. Fifteen patients were male and nine were female.

The number of days from the onset of the rapidly spreading infection until its recognition varied from 2 to 15 days, with an average incubation period of 5 days.

The highest temperature recorded was 107.4 F and the lowest 100 F, with an average of 103.2 F. The white blood cell count varied from 6200 to 48,000, with an average of 21,500 per cubic millimeter.

Of the 24 patients, 8 were known or were proved to have diabetes mellitus.

Bacteriologic studies revealed the bacterial flora to be mixed in all cases. The frequency with which the various aerobic and anaerobic bacteria were encountered is shown in Table 2.

The average number of types of bacteria found in each case was 3.3. The aerobic bacteria most frequently found were E. coli and the nonhemolytic Streptococcus. Of the anaerobic bacteria, the anaerobic Streptococcus and Bacteroides melaninogenicus were the most frequently seen.

The following case represents the development, course, and nature of acute nonclostridial crepitant cellulitis.

CASE 1.—A 37-year-old Negro man, a known diabetic, was admitted on Feb. 28, 1944, with a history of an infected callus on the lateral aspect of the right foot following partial excision one week prior to admission. The wound had then become painful, swollen, and markedly tender. Examination revealed an acutely ill, adult Negro, whose temperature was 102.6 F, pulse 96, and respirations 26. There was a deep ulcer of the lateral aspect of the right foot which exuded foul-smelling pus, and the entire foot and lower one-third of the leg showed marked edema and redness. Lymphangitic streaks were easily visible to a point above the knee. His white blood cell count was 22,150 cells per cubic millimeter, red blood cell count 3,030,000, and hemoglobin 13.0 gm. %.

On the day after admission, incision and drainage of the involved area were done, and a large amount of gas was found in the grayish-black subcutaneous tissues about the ulcer. Postoperatively, the wounds were irrigated with sodium hypochlorite solution U. S. P. (Dakin's solution) every three hours, and the patient was given penicillin and sulfadiazine systemically. Smears made of the pus showed numerous streptococci but no bacillus. Cultures revealed the presence of aerobic nonhemolytic Staphylococcus aureus var. albus, the viridans type of Streptococcus, Corynebacterium pseudodiphtheriticum, and S. sendai, as well as the anaerobic Bacteroides melaninogenicus and Staphylococcus. Two days after the operation the crepitation had extended 6 to 8 in. above the malleoli, and the signs of toxemia had increased. Believing the infection to be an uncontrolled gas gangrene, his surgeon did a guillotine amputation

TABLE 2.—*Frequency of Aerobic and Anaerobic Bacteria*

| | |
|---|---|
| I. Aerobic | |
| A. Coliform bacteria | |
| 1. Escherichia coli | 9 |
| 2. Proteus vulgaris | 5 |
| 3. Alcaligenes faecalis | 1 |
| 4. Salmonella sendai | 1 |
| 5. Paracolon bacillus | 2 |
| 6. Aerobacter aerogenes | 2 |
| B. Pyogenic bacteria | |
| 1. Nonhemolytic Streptococcus | 12 |
| 2. Hemolytic Streptococcus | 7 |
| 3. Unidentified Streptococcus | 4 |
| 4. Hemolytic Staphylococcus aureus | 4 |
| 5. Staphylococcus aureus var. albus | 3 |
| C. Corynebacterium pseudodiphtheriticum | 5 |
| II. Anaerobic | |
| A. Cocci | |
| 1. Nonhemolytic Streptococcus | 6 |
| 2. Nonhemolytic Staphylococcus | 2 |
| 3. Unidentified | 4 |
| B. Bacteroides | |
| 1. Bacteroides melaninogenicus | 9 |
| 2. Bacteroides funduliformis (Bacillus thetoides) | 1 |
| 3. Bacteroides fragilis | 1 |
| 4. Unidentified | 2 |
| C. Nonsporulating bacilli | |
| 1. Corynebacterium pseudodiphtheriticum | 1 |
| 2. Unidentified | 2 |

at the level of the midthigh on March 3. Examination of the amputated leg showed the subcutaneous tissues to be edematous, grayish-black in color, and crepitant up to the knee, but the muscles were not involved. Cultures of the pus were consistent with previous ones except for the anaerobic Staphylococcus. Immediate and striking improvement occurred after operation.

## Methods of Treatment

The treatment depends primarily on the recognition that acute nonclostridial crepitant cellulitis is not gas gangrene and that the infection is confined to the epifascial subcutaneous fat. Early and radical incision of the skin and subcutaneous tissue to points beyond the furthermost limits of the infection is required for control of the infection.

Systemic antibiotic therapy is used in large doses and, because of the polymicrobic etiology, the regimen should include penicillin and one of the tetracycline type of drugs or chloramphenicol.

After adequate incision and drainage of the affected tissues has been done, local treatment of the diseased tissues with zinc peroxide is indicated. This medicament may be applied in the form of a creamy suspension or a stable ointment.

The more successful application of early diagnosis and vigorous treatment is illustrated in the following case reports.

CASE 2.—A 58-year-old white man was admitted on May 19, 1946, for operative repair of a strangulated recurrent left inguinal hernia associated with cramping abdominal pain, vomiting, and constipation. He had had a bilateral hernioplasty in 1925, a right hernioplasty in 1930, and a left hernioplasty in 1933.

His temperature was 98.2 F, pulse 96, and respirations 22. Other findings were within normal limits except for bilateral inguinal scars and a firm, tender mass, measuring 5×10 cm., over the medial third of the left inguinal ligament. Peristalsis was hyperactive. The white blood cell count was 8600 per cubic millimeter; hemoglobin was 11.5 gm. %, and urinalysis was essentially normal. Roentgenograms of the abdomen indicated small-bowel obstruction.

An operation on the day of admission revealed a small Richter's hernia, which was strangulated in a femoral sac. The bowel was markedly cyanotic but viable. Twelve hours after hernioplasty, his temperature rose to 100.4 F. The wound became markedly tender, and subcutaneous crepitation was noted at the superior angle. On May 23, the operative wound was reopened, and radical incision and drainage of the surrounding cellulitic area were done. The skin was undermined throughout the full extent of the infection and the incision carried into the adjacent normal tissues. The subcutaneous fat over the left abdominal wall was found to be grossly infected, gray, malodorous, and necrotic to the level of the 10th rib superiorly, to the symphysis and umbilicus medially, to the inguinal ligament inferiorly, and to a point 5 cm. beyond the anterior superior spine laterally. Zinc peroxide ointment dressings were applied to the wounds, and streptomycin, in doses of 200 mg. every three hours, was given intramuscularly for 9 days, followed by 100 mg. every three hours for 10 days. The infection subsided, and the granulating wound assumed a healthy appearance within 14 days. Thiersch grafts were successfully applied to the granulating wounds on June 14 and on June 28, after which complete healing promptly occurred.

CASE 3.—A 65-year-old Negro man was admitted on Oct. 30, 1954, because of abdominal pain, nausea, and vomiting of two days' duration. He was known to have diabetes mellitus and gave a history of fatty food intolerance.

His temperature was 100 F, pulse 108, and respirations 24. Other findings were noncontributory to the diagnosis of his acute illness except that his abdomen was slightly tender. In the right upper quadrant an acutely tender, tensely distended gallbladder could be palpated. His white blood count was 11,400 per cubic millimeter and hemoglobin 14 gm. %. Urinalysis showed a trace of sugar but was otherwise normal. A serum amylase of 444 Somogyi units was reported. X-ray of his abdomen was essentially normal.

Because of the acutely distended gallbladder, cholecystectomy was done about four hours after admission. Exploration of the common duct revealed several stones, which were likewise removed. Postoperatively, he developed moderate hypotension, which was treated with an infusion of levarterenol (Levophed) bitartrate for about 48 hours, at which time he improved and the infusion was discontinued.

On his fifth postoperative day he complained of pain in his leg at the site of previous intravenous infusions. Examination revealed necrosis of the skin of his lower leg and massive cellulitis of the leg from the ankle to the upper thigh, with much subcutaneous emphysema. His temperature was 100.8 F, pulse 110, and respirations 28. At this time his white cell count had risen to 19,000 per cubic millimeter and his hemoglobin had fallen to

Fig. 1 (Case 3).—Postoperative appearance of left lower extremity after excision of necrotic skin of lower leg and radical incision and drainage of crepitant cellulitis of the thigh. Note thin, watery drainage from thigh wounds and dark-grayish appearance of subcutaneous fat.

11.5 gm. %. X-ray of the extremity showed subcutaneous air.

He was taken to the operating room, and excision of the necrotic skin (Fig. 1) of the lower leg and radical decompression drainage of the subcutaneous tissues of the entire thigh were done. The infectious process was limited to the epifascial structures and was controlled with the use of zinc peroxide ointment locally. Aqueous penicillin in doses of 6,000,000 units daily and 500 mg. of oxytetracycline (Terramycin) were given intravenously every six hours. Cultures revealed beta hemolytic Streptococcus, E. coli, and S. aureus var. albus. His recovery followed, but morbidity was prolonged because of required skin grafting. He was discharged on his 126th hospital day.

Case 4.—A 23-year-old taxi driver was admitted to the hospital on Jan. 25, 1958, after having been stabbed in the chest and abdomen in a fight. He apparently had previously been well.

Examination revealed him to be drunk and uncooperative. His blood pressure was 90/60, pulse 120, and respirations 24. Stab wounds were noted in the sixth and eighth interspaces of the left midaxillary line, in the midepigastrium, in the right midabdomen, through which omentum protruded, and in the left flank. His abdomen was tender, and no peristaltic sounds could be heard. X-ray of the chest was normal.

Hypotension was controlled with whole-blood transfusions, and he was taken to the operating room, where a laparotomy revealed three stab wounds of the ascending colon, one wound of the transverse colon and two wounds of the descending colon, and a stab wound of the liver, the spleen, and the left leaf of the diaphragm. The wounds of the colon, diaphragm, and liver were closed, and a splenectomy was done.

Postoperatively, he was treated with gastric suction, 3,000,000 units of penicillin and 1.5 gm. of chloramphenicol (Chloromycetin) intravenously daily. He continued to have fever, with temperature elevation to 100, daily, and a leukocyte count as high as 18,000. On the eighth postoperative day he developed left pleural fluid and pneumothorax, which were relieved by thoracentesis. On the 10th postoperative day examination of the abdomen revealed the presence of a subcutaneous emphysematous cellulitis, extending from the pubis to the lower rib cage on the left side, and a probable lower abdominal mass. A radical incision and drainage of the crepitant cellulitis were done that day, and an unsuccessful attempt to drain the pelvic abscess was made (Fig. 2). Zinc peroxide ointment was applied to the necrotic, gas-containing, cellulitic areas. Prior to drainage, his white cell count was 40,000; temperature 102 F.

Following this operation his temperature decreased slightly, and his leukocyte count decreased gradually. On the 14th hospital day the pelvic abscess was drained suprapubically of 1000 cc. of foul pus. Following this there was gradual return of temperature, pulse, and white cell count to normal. On the 23d hospital day he was afebrile, was taking a regular diet, and his wounds were clear of invasive infection and beginning to heal.

## Results of Treatment

In 21 out of the 24 patients studied, the spread of the infectious process was completely arrested by the treatment described above. In three instances the measures used failed to halt the spread of the infections. In one instance, prior to the advent of antibiotics, the infection spread rapidly from the neck to the mediastinal compartments in spite of vigorous treatment. Another pa-

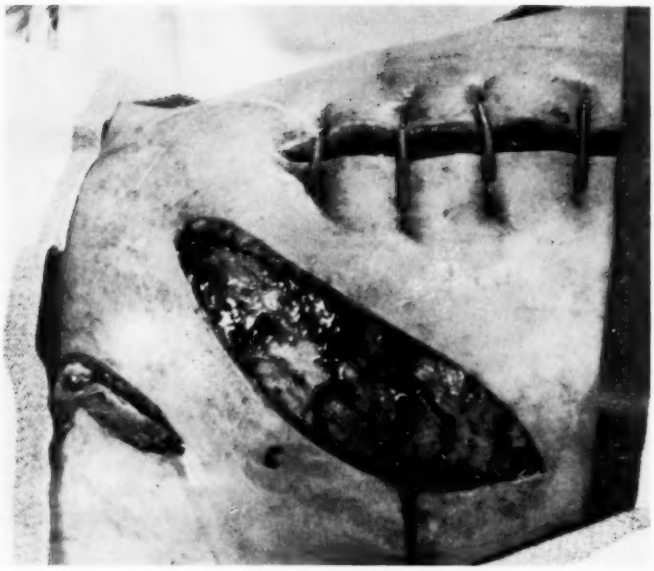

Fig. 2 (Case 4).—Appearance of abdominal wall after radical incision and drainage of acute nonclostridial creptitant cellulitis. Treatment for a stab wound of the abdomen had been done 10 days previously. The subcutaneous fatty tissues have been undermined from the midline incision in the left flank.

tient received vigorous antibiotic treatment, though his surgical treatment reflected some timidity, since three separate attempts were required for adequate drainage, and death resulted from the effects of his infection. A third patient was 89 years old, and she died on the eighth day of illness with her infection slowly advancing in spite of proper and vigorous treatment measures.

Four other patients died after their infection was apparently controlled: one of peritonitis and interloop abscess on the 21st postoperative day; one as a result of myocardial infarction on the 2d postoperative day, and another of similar disease on the 34th day. The seventh death in the 24 patients resulted from a cerebrovascular occlusion on the 24th postoperative day.

The period of morbidity in the surviving patients averaged more than 60 days. The advancing infective process was controlled within 7 to 10 days, the remainder of the period being required for the various reconstructive procedures and complete healing.

In eight of the patients, large doses of systemic chemotherapy were administered for the associated disease for periods of 2 to 15 days prior to the onset of acute crepitant cellulitis. In these cases the infection developed in spite of existing vigorous antibiotic treatment, and control of the disease required prompt and vigorous surgical measures.

The use of zinc peroxide ointment or cream was highly desirable and allowed the development of clean, granulating wounds within five to seven days. Similar results occurred in two cases in which hydrogen peroxide was used, but this method proved very cumbersome.

## Analysis and Comment

These 24 cases permit an appreciation of the character of acute nonclostridial crepitant cellulitis. The lesion characteristically is a rapidly spreading, necrotizing infection of the skin and epifascial connective tissues of the perineum, abdominal wall, buttocks, lower extremities, thorax, or neck, which are easily contaminated by discharge from the intestinal, genitourinary, or respiratory tract. This infection usually develops when invasion of the subcutaneous tissues occurs either primarily, from contamination of an

operative or accidental wound, or secondarily, from a preexisting localized infection. The process extends rapidly and superficially over wide areas of the body, usually without involvement of the structures beneath the deep fascia. The presence of preexisting necrosis or foreign bodies seems to favor its development and spread.

The essential pathology is a wet inflammation of the subcutaneous tissues, which progresses to necrosis with crepitation within two to five days after the onset. In those cases in which Bacteroides melaninogenicus was found, the subcutaneous tissues usually presented a grayish-black color. Thrombosis of the nutrient vessels of the skin is a prominent histologic finding.

It is probable that the presence of markedly elevated blood sugar permits or encourages the growth of a bacterial infection capable of producing gas, and the defense factors against the rapid spread of infection in diabetics are impaired.

No single type of etiologic agent was consistently present, and several groups of bacteria seemed to be capable of producing this lesion. The various types of organisms suggested that a symbiotic or synergistic relationship is active in the process. The nonclostridial bacteria which apparently were capable of causing the infection under certain conditions included some strains of the coliform group, particularly E. coli, the anaerobic Gram-negative bacilli of the Bacteroides group, such as B. melaninogenicus and B. funduliformis (B. thetoides), and the anaerobic Streptococcus. In other cases which were similar clinically, cultures revealed the same mixed type of flora, in addition to Clostridium welchii or one of the other clostridia. These cases were not included in this report, although it seemed doubtful that the clostridia contributed to the severity of the process. It has been impossible to prove by animal experimentation that the anaerobic Streptococcus or B. melaninogenicus is the causal bacterium, since these organisms have been uniformly avirulent for experimental animals in our experience. However, there is strong presumptive evidence that these organisms are virulent for human beings.[1] The fact that some members of the coliform and Bacteroides groups are pathogenic and gas-producing in experimental animals, has been established, however, and there is experimental evidence of marked synergistic activity of groups of intestinal bacteria.[2,3,8]

The first symptom was pain, which usually persisted or developed in and about the wound. Within 24 hours there was an elevation of temperature to 101 to 104 F, with a corresponding increase in the pulse and respiratory rates. The pain preceded by one to three days any obvious swelling or erythema of the overlying skin. As the cutaneous swelling progressed, the pain increased, exquisite tenderness to the slightest touch developed, and crepitation became perceptible. Early in the infection the patient's general condition frequently appeared to be good, but, as the lesion extended, marked evidence of toxemia became evident, with dehydration, temperature as high as 105 to 107 F, a weak and thready pulse, and prostration. The white blood cell count increased, and in one instance it reached 48,000 per cubic millimeter. Anemia with falling red blood cell count and hemoglobin level, usually necessitated frequent blood transfusions.

The clinical course is characterized by the rapidity of extension of the process, almost one-half of the wall of the torso being involved within four to five days in some instances.

Early diagnosis, essential for most effective treatment, is based on the history and clinical findings. The prognosis is good in the patients treated promptly and adequately. Since delay in diagnosis permitted further spread of the infection and increased the duration of morbidity, early investigation of wounds in questionable cases is obvious. Roentgenograms for soft-tissue detail have aided somewhat in the recognition of gas and in determining the limits of spread in areas not accessible to digital examination.

The principal method of treatment for this condition is early and adequate surgery, consisting of radical decompression of the involved area by long and wide incisions through the skin and subcutaneous tissues down to the superficial layer of the deep fascia and peripherally into healthy tissue beyond the furthermost limits of the lesion. The process is one of pus under pressure; the drainage is necessarily radical to decompress all the involved areas. Recognition of the extent of the infection at times may be difficult, but the skin erythema and the presence of a grayish discoloration of the epifascial subcutaneous fat are characteristic of diseased tissue.

In some instances, it was possible to drain the area effectively by a single linear incision with undermining of the skin flaps. Since radical incisions arrested the process, amputation is usually unnecessary, and the one in Case 1 was done on the basis of a mistaken diagnosis of gas gangrene.

Antibiotic therapy is indicated only as an adjuvant to surgery. Because of the mixed bacterial flora, parenterally administered penicillin in doses of 500,000 units every six hours and tetracycline or chloramphenicol in doses of 500 mg. every six hours are recommended.

Daily dressings of the wounds with zinc peroxide ointment is helpful in the control of the infection, which usually is so extensive that fever, elevation of pulse rate, and signs of toxemia persist for three or more days postoperatively. After control of the infection and development of clean granulation tissue, skin grafting is done.

Important general supportive therapy includes intravenous fluids for adequate hydration and electrolyte intake, repeated whole-blood transfusions, and rest.

## Summary

The causes of cutaneous crepitation in the presence of infection are reviewed. Twenty-four cases of acute nonclostridial crepitant cellulitis are reported, and their clinical and bacteriologic features are analyzed.

Cincinnati General Hospital, 3231 Burnet Ave. (29).

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## DISCUSSION

DR. W. R. CULBERTSON, Cincinnati: One other comment is that of the 12 cases which have been studied in this survey since the advent of the wide use of antibiotics, 8 have been in patients who have been receiving, for other disease, very adequate doses of usually two, and sometimes three, antibiotics; so this infection may occur in spite of the antibiotic prophylaxis therapy.

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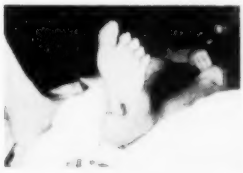

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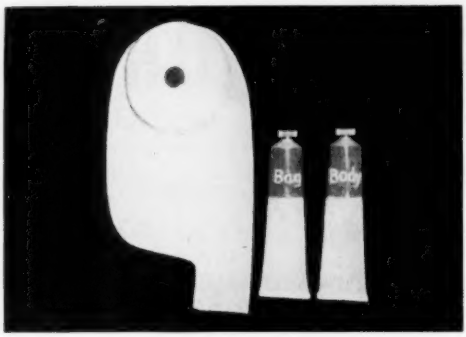


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**BONE CYST . . . 4 aspects**

**Radiograph** *(upper left)* of bone cyst of the fibula. The lesion has its characteristic location in the end of the shaft and does not transgress the plate.

**Photograph** *(upper center)* of external surface of upper end of fibula resected because of the presence of a bone cyst. The contour of the cystic area is expanded, and two healed fracture lines are to be noted.

**Photograph** *(upper right)* of transected specimen showing the lesion illustrated above, center. The cyst cavity contains considerable organizing blood, which was present because of recent fracture.

**Photomicrograph (x 3)** *(left)* showing topography of the fibular cyst. From above down, one notes epiphysis, epiphyseal cartilage plate, and cyst wall abutting upon the metaphyseal spongiosa and plate area.

For data on Nonossifying Fibroma, turn page.

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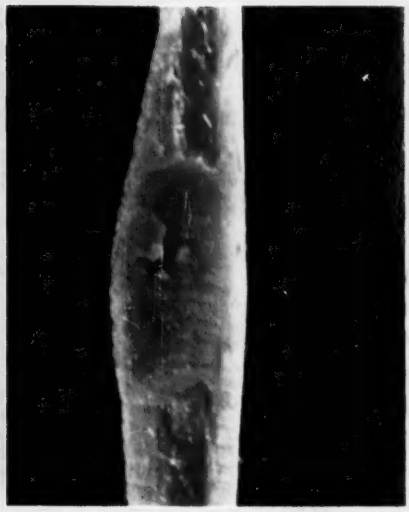
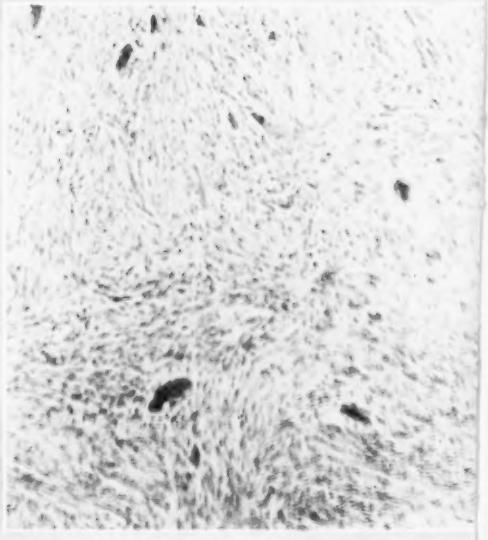


## NONOSSIFYING FIBROMA . . .
## 3 aspects

**Radiograph** *(upper left)* of a nonossifying fibroma in the shaft of a fibula of a boy of 8 years. The lesional area appears somewhat loculated.

**Photograph** *(upper right)* of segment of fibula (cut longitudinally) containing the lesion shown in the preceding radiograph.

**Photomicrograph (x 15)** *(right)* showing the general pattern characteristic of the lesional tissue of nonossifying fibroma. The stromal cells are spindle-shaped and whorled, and intermingled with small numbers of giant cells.



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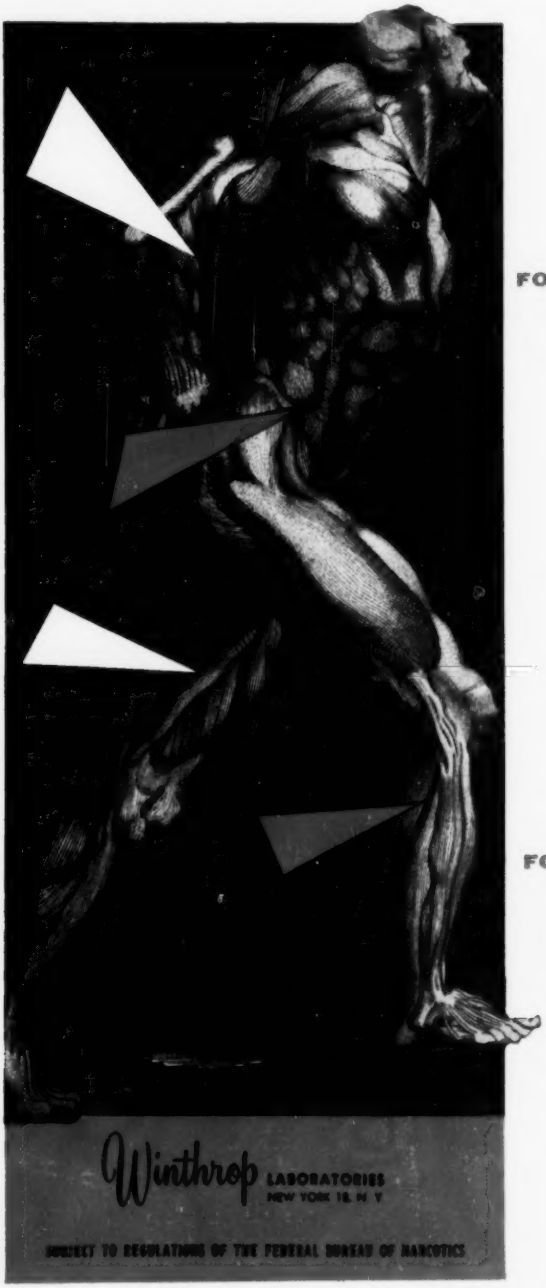


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